FDA Advisory Committee Joint Meeting: Reproductive Health Drugs; Drug Safety and Risk Management

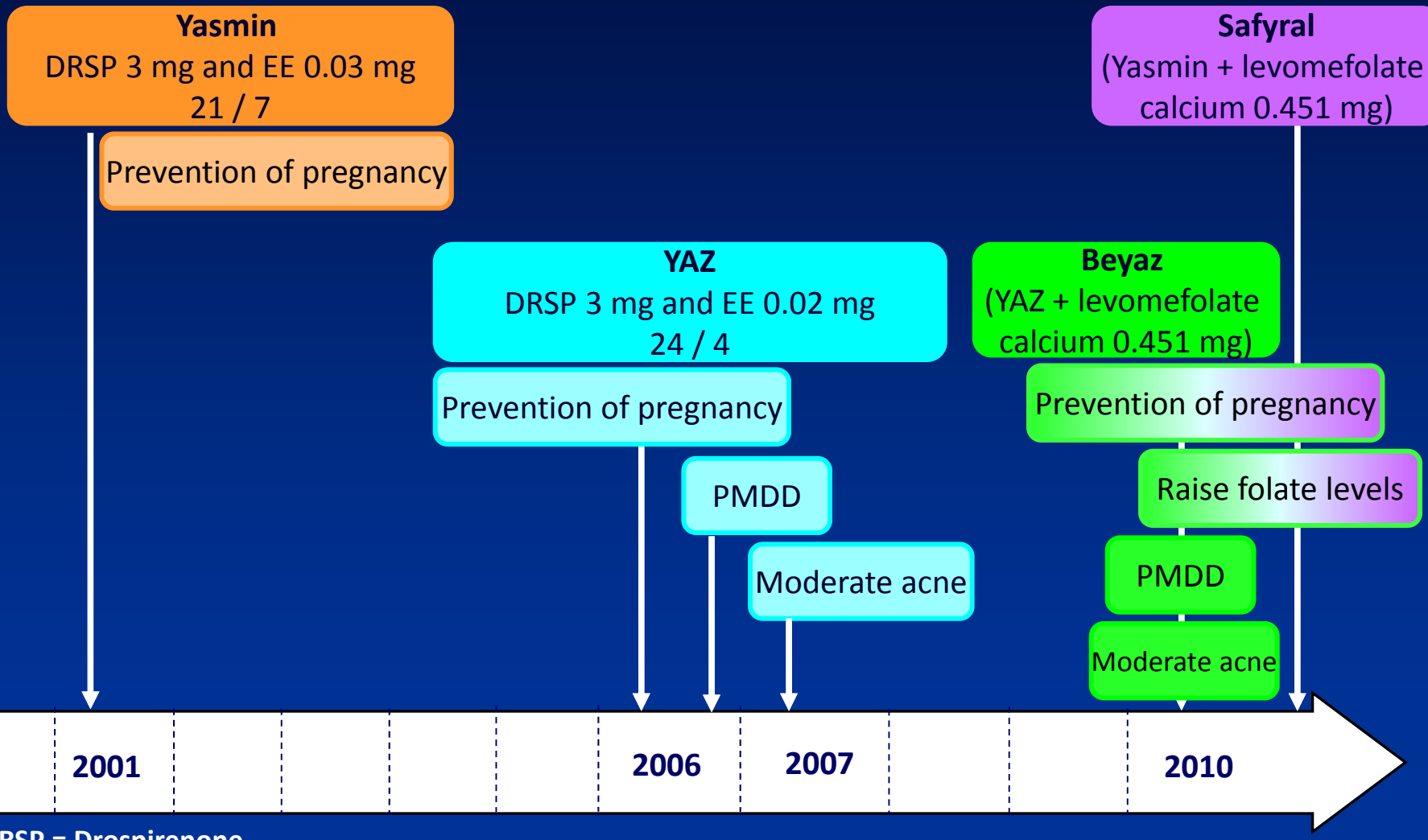
December 8, 2011

Bayer HealthCare Pharmaceuticals, Inc.

Introduction and Overview of Sponsor's Presentation

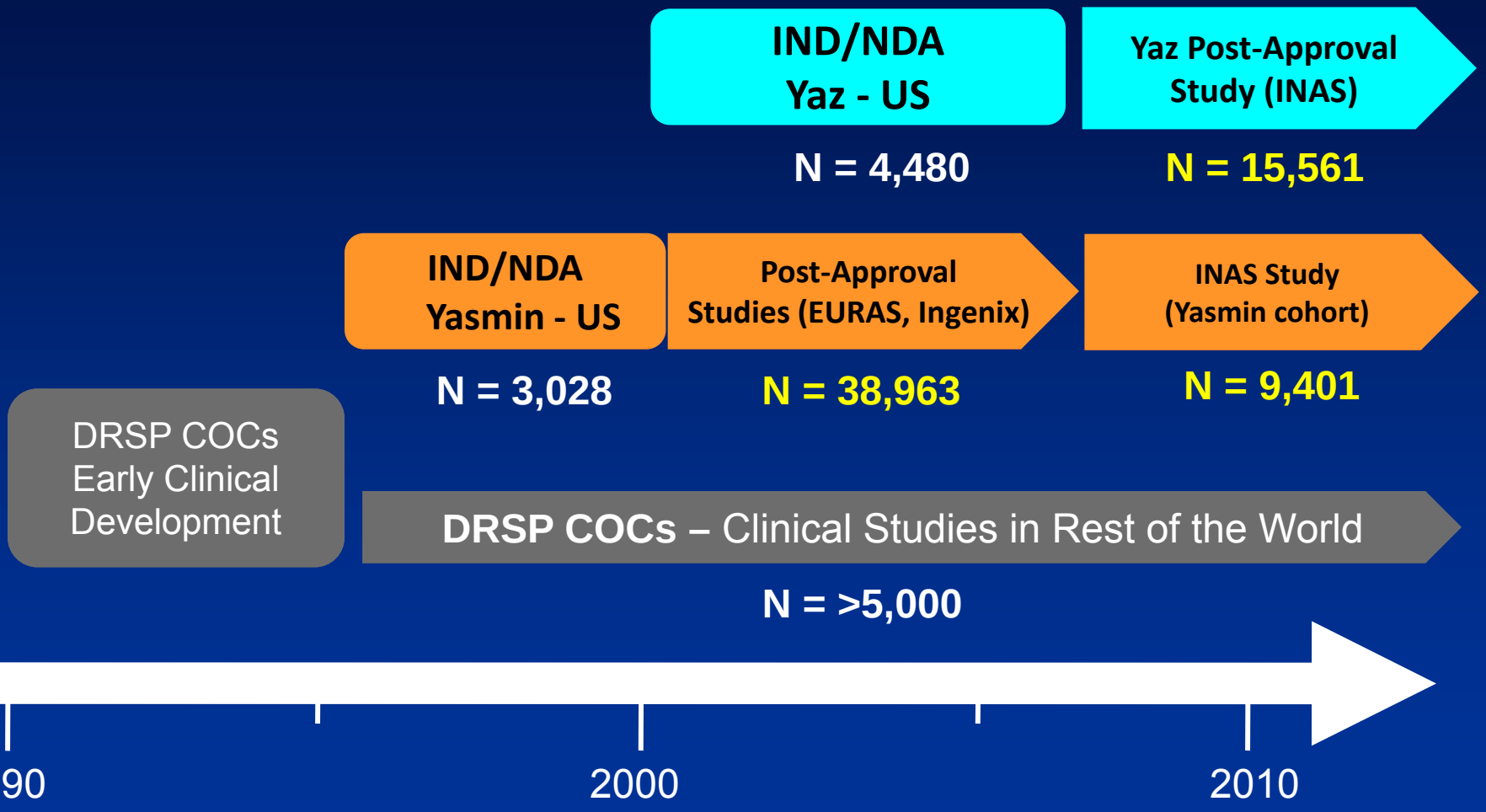
John Talian, PhD
Vice President and US Head,
Global Regulatory Affairs
Bayer HealthCare Pharmaceuticals, Inc.

Drospirenone-containing Combined Oral Contraceptives – US Approvals and Indications



DRSP = Drospirenone
EE= Ethinyl Estradiol

Development Program for Drospirenone-containing COCs



N = # of subjects
COC = Combination Oral Contraceptives

Presentation Outline

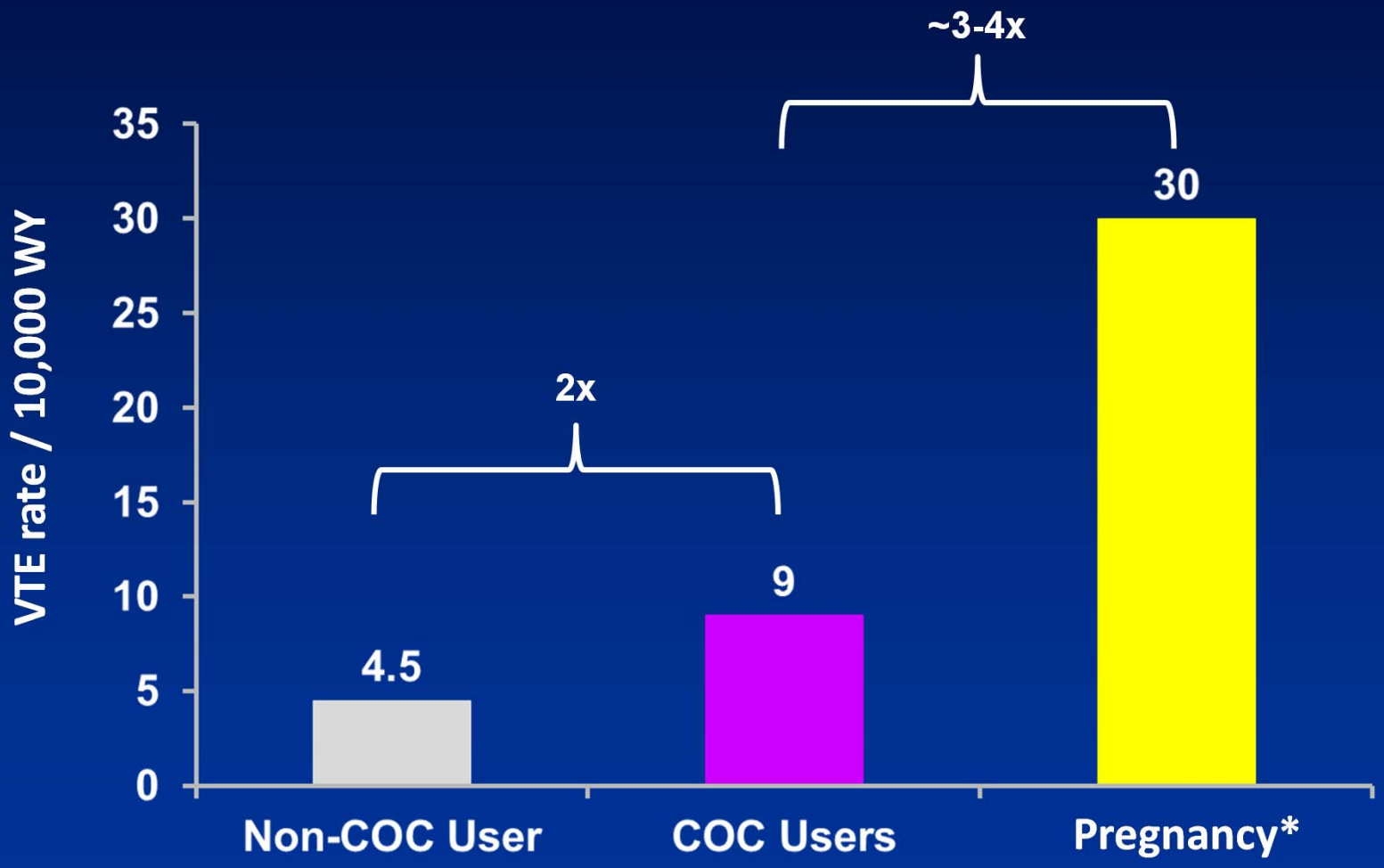
• Post-Approval Safety Studies	Leo Plouffe Jr, MD, FACOG Vice President, WHC US Medical Affairs Bayer HealthCare Pharmaceuticals, Inc.
• Assessment of the Published Observational Studies	David Grimes, MD, FACOG Clinical Professor, Department of OB/GYN University of North Carolina School of Medicine
• Review and Remarks: FDA-Funded Study First Phase	Robert Makuch, PhD Professor, Biostatistics Yale University School of Medicine
• A Clinician's Perspective	Andrea Lukes, MD, MHSc, FACOG Carolina Women's Research and Wellness Center
• Final Comments	Leo Plouffe Jr, MD, FACOG

Post-Approval Safety Studies

Leo Plouffe Jr, MD

Vice President, US Medical Affairs
Women's HealthCare
Bayer HealthCare Pharmaceuticals, Inc.

VTE Rates in Reproductive Age Women



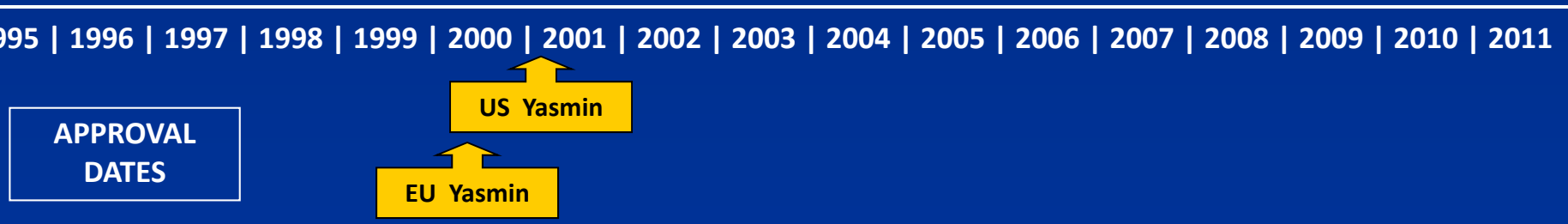
WY = Women-years

Heit et al 2005, Ann Intern Med 143, 697-706

Post-Approval Commitment Studies – Yasmin

Ingenix
(FDA)

EURAS
(EMA)



EMA = European Medicines Agency

Sound Principles for Observational Studies

- Protocol, Amendments and Full Statistical Analysis Plan completed prior to data analysis
- Reproducible methods and results
- Demonstrated comparability among treatment groups on key risk factors
  - Availability and accuracy of information from data source

Comparing VTE Risk Between COCs: Biases to be Considered

- Duration of use / pattern of use
- Attrition of susceptibles / healthy user effect
- Prescription bias (Channeling)
- Validity of diagnosis for VTE
- Referral / diagnostic bias for VTE

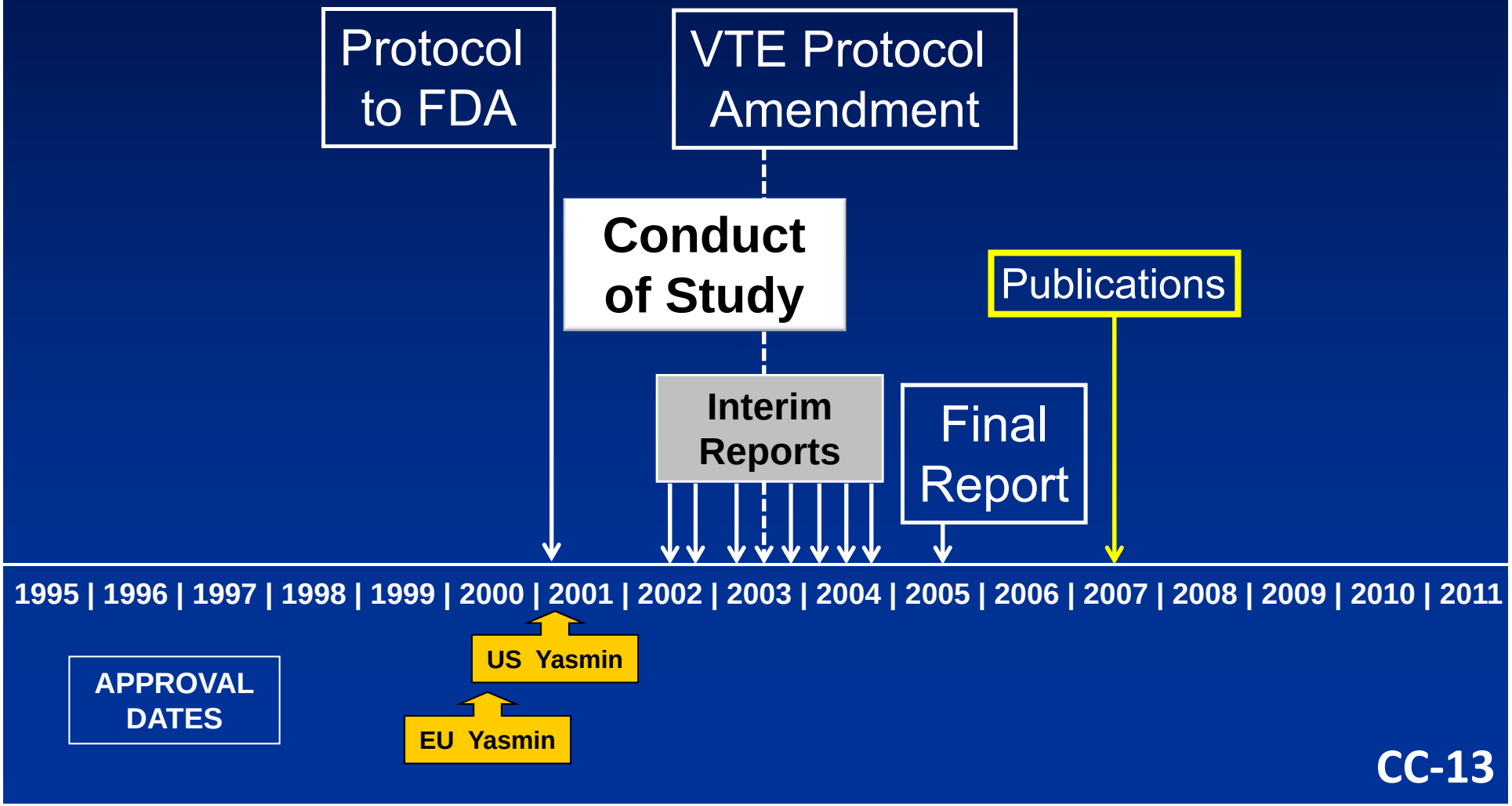
Post-Approval Safety Studies with Yasmin

Venous Thromboembolic Events

Post-Approval Safety Studies – Yasmin

Study	Type of Study	Post-Approval Commitment (Regulatory Authority)
Ingenix	Prospective cohort	Yes (FDA)
European Active Surveillance Study (EURAS)	Prospective cohort	Yes (EMA)
Long-Term Active Surveillance Study (LASS)	Prospective cohort	No
German Case-control Study	Case-control	No
Prescription Event Monitoring (PEM)	*Non-comparative Surveillance*	*No*

Ingenix Study: US Post-Approval Commitment



Ingenix: Study Design

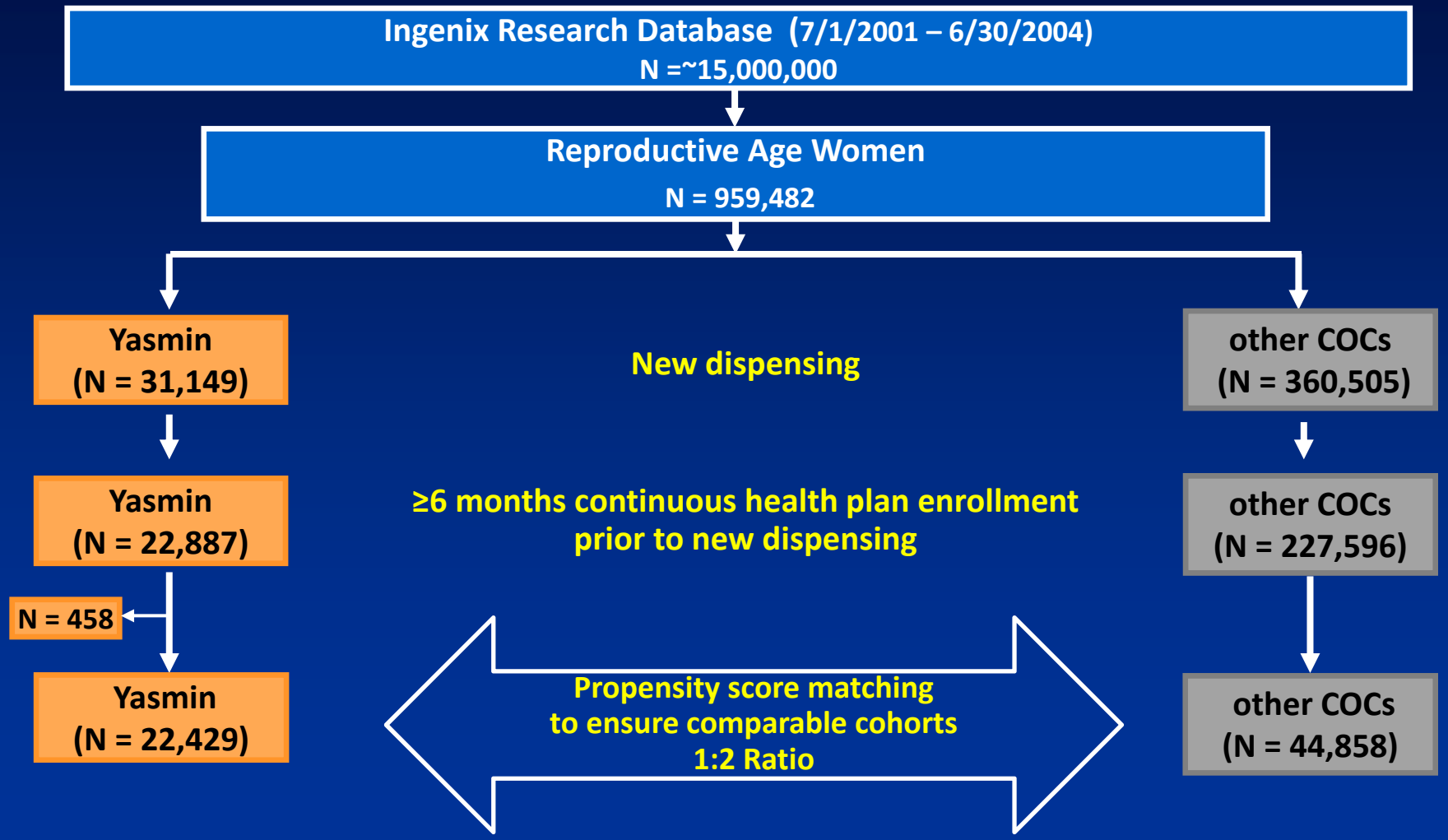
- US claims-based, observational cohort study
- N = 67,287; 41,656 WY

Cohort	N	WYs
Yasmin	22,429	14,081
Other COCs	44,858	27,575

- Average follow-up is 7.6 months
- Several outcomes identified in protocol
  - VTE is focus of this presentation

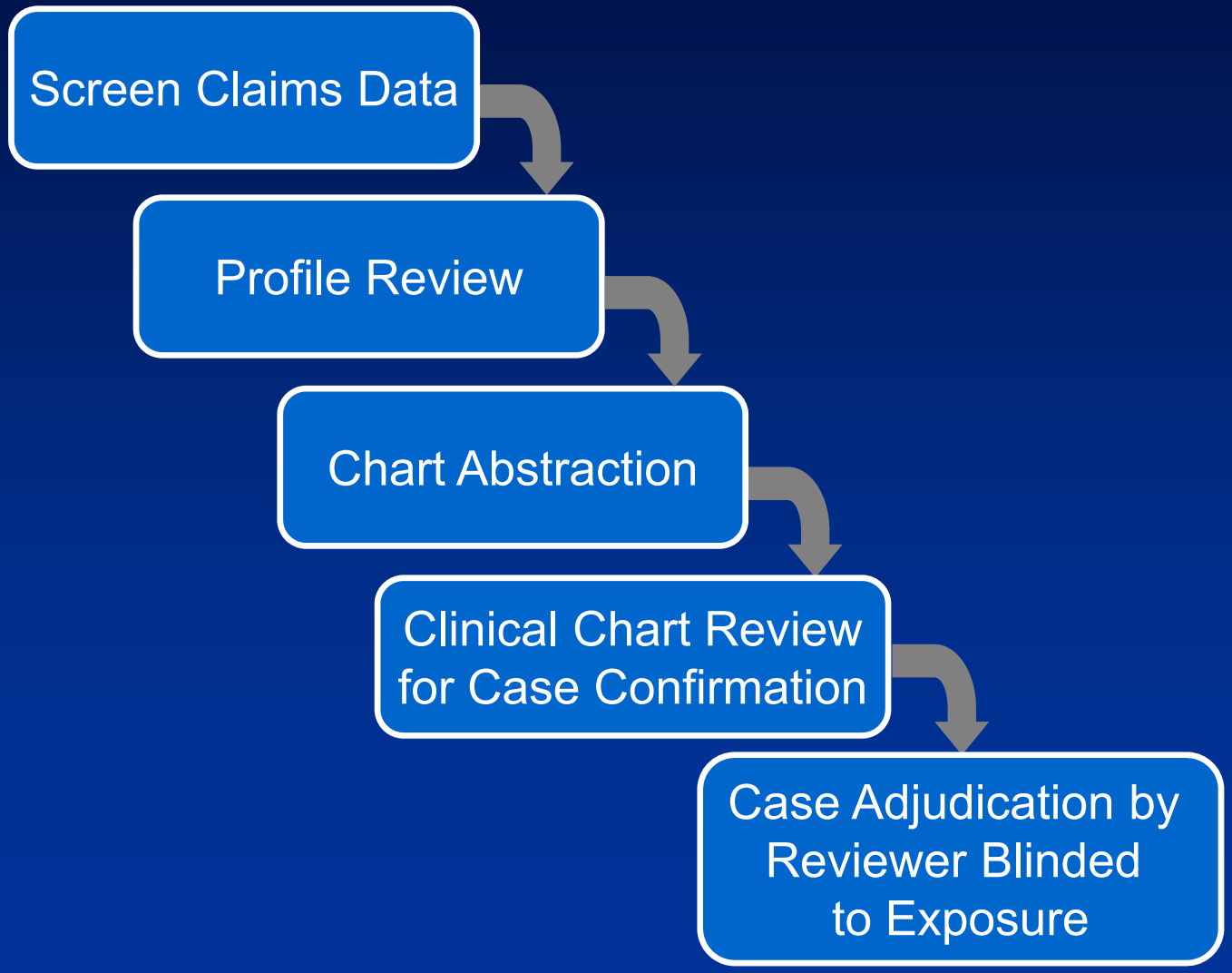
Seeger JD et al. *Obstet Gynecol*. 2007;110:587-593.

Ingenix: Cohort Creation



Adapted from Seeger JD, et al. *Obstet Gynecol.* 2007;110(3):587-593

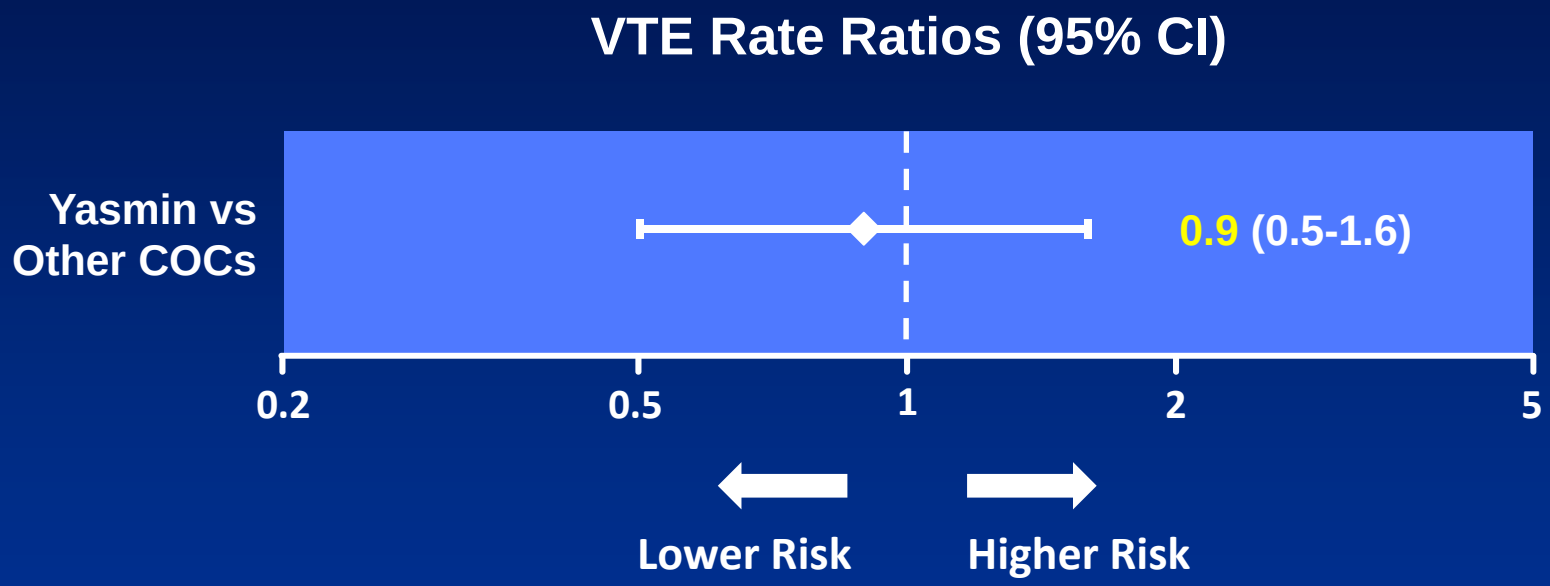
Ingenix Study: Validation Process for Suspected VTE Cases



Ingenix Study: Strengths & Limitations

- Strengths
  - VTE confirmation based on clinical chart review and blinded adjudication
  - Balance of cohort baseline risk through propensity score matching (and record ascertainment in validation studies)
  - Cohorts matched based on patterns, timing and duration of exposure (only users after at least 6 months without COC)
- Limitations
  - Potential for referral and diagnostic bias
  - No direct adjustment for BMI or smoking
  - Unable to distinguish first-ever start from new start or restart

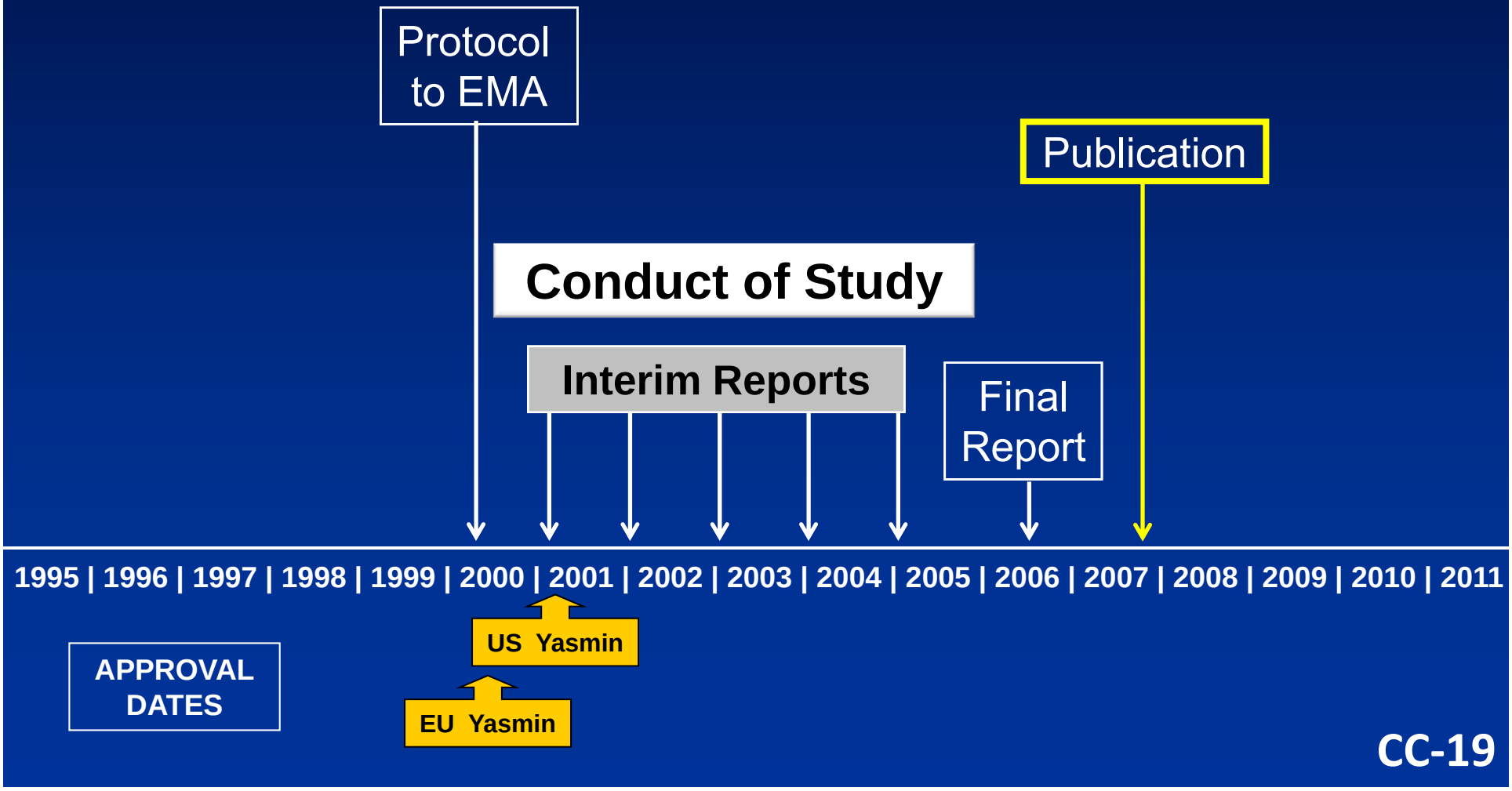
Ingenix Study: Risk of VTE



Yasmin: 14,081 WY; 18 VTE events, Incidence rate 13/10,000 WY (95% CI: 0.8-2.0)
Other COCs: 27,575 WY; 39 VTE events, Incidence rate 14/10,000 WY (95% CI: 1.0-1.9)

CI = Confidence Interval
ITT (Intent-to-treat) analysis among matched cohorts
Rate ratio calculated using a proportional hazards model

EURAS Study:
EMA Post-Approval Commitment



EURAS: Study Design

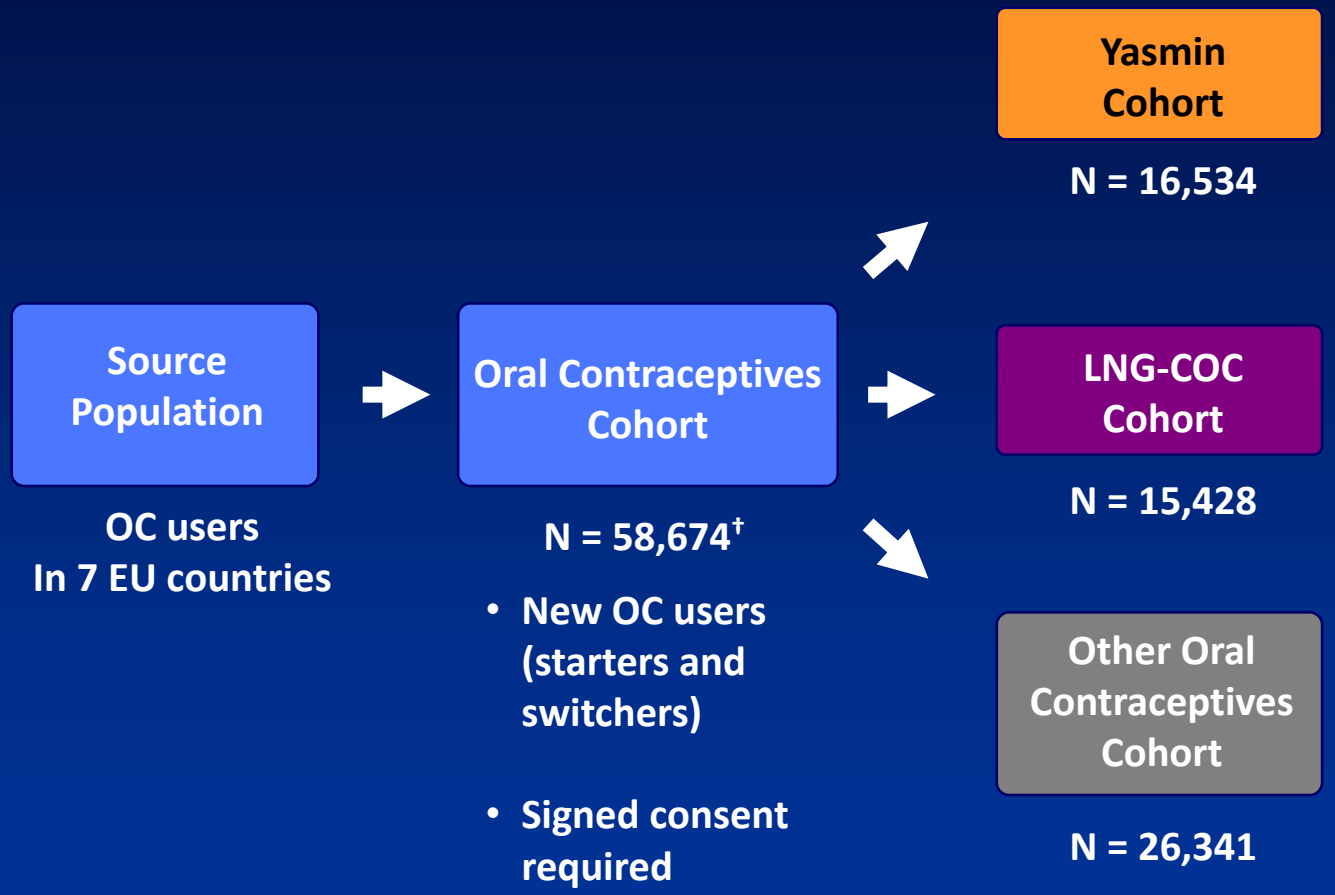
- Multinational, prospective, noninterventional, controlled, cohort study*
- N = 58,674; 142,475 woman-years of observation

Cohort	N	WY of Exposure
Yasmin	16,534	28,621
Levonorgestrel COCs	15,428	31,415
Other OCs	26,341	52,623
Non-oral Hormonal Contraceptives (NOHC)	371	4,049

- Follow-up 1.5 – 5 years
- Several outcomes identified in protocol
  - VTE is focus of this presentation

Dinger JC et al. *Contraception*. 2007;75:344-354. / * ClinicalTrials.gov: NCT00302848

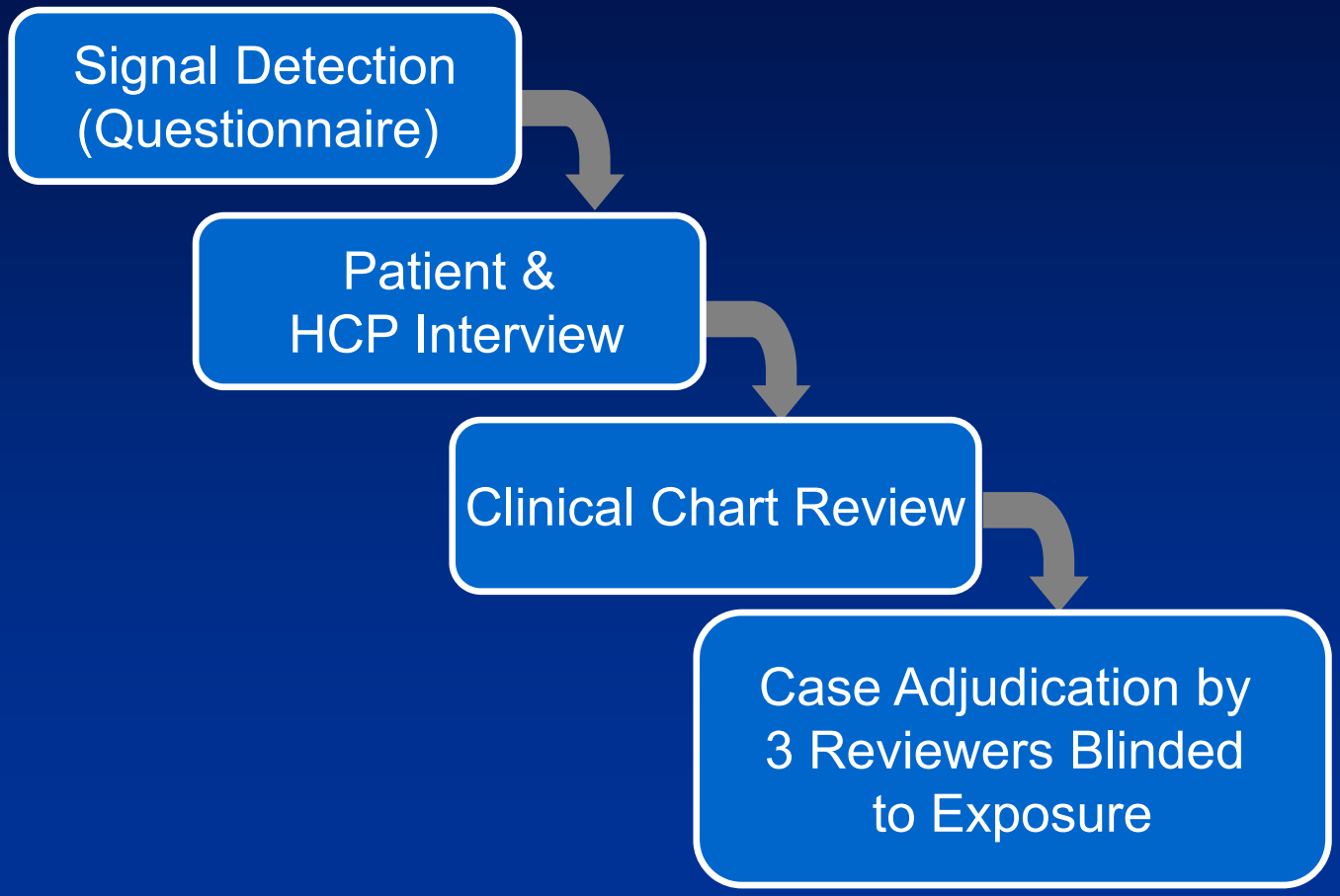
EURAS: Study Design



† This number includes a cohort of non-oral hormonal contraceptive users (NOHC, N=371)

Dinger JC et al. *Contraception*. 2007;75:344-354.

EURAS Study:
Validation Process for Suspected VTE Cases

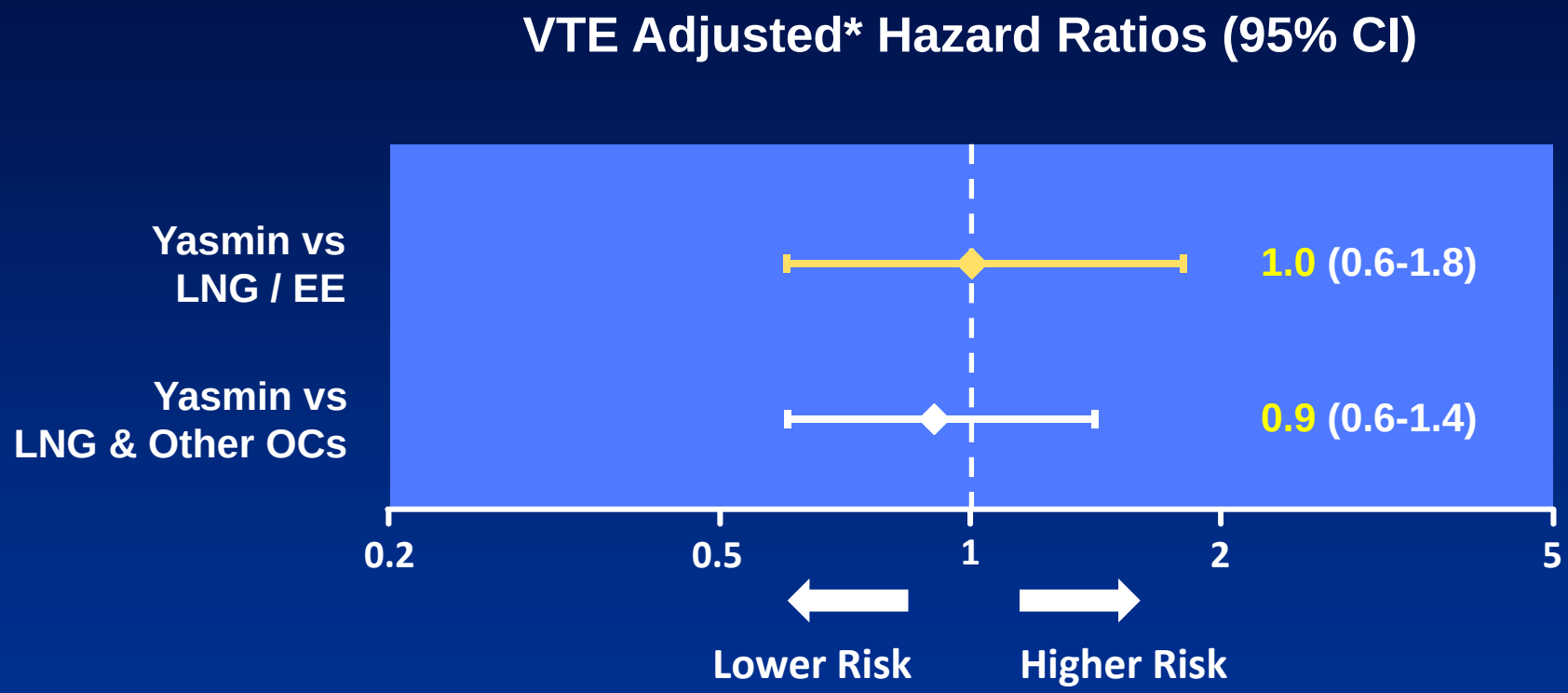


HCP = Healthcare Provider

EURAS Study: Strengths & Limitations

- Strengths
  - Adjusted for pre-defined confounding factors (including age, BMI, personal and family history of VTE)
  - Prospective cohort design that inherently controls and adjusts for duration and pattern of OC use, including first-time ever users
  - VTE cases confirmed by chart review and blinded adjudication
- Limitations
  - Events and exposure self-reported by subjects and may be influenced by memory
  - Active surveillance process with prompted recall
  - Inclusion in study required patient consent

EURAS Study: Risk of VTE

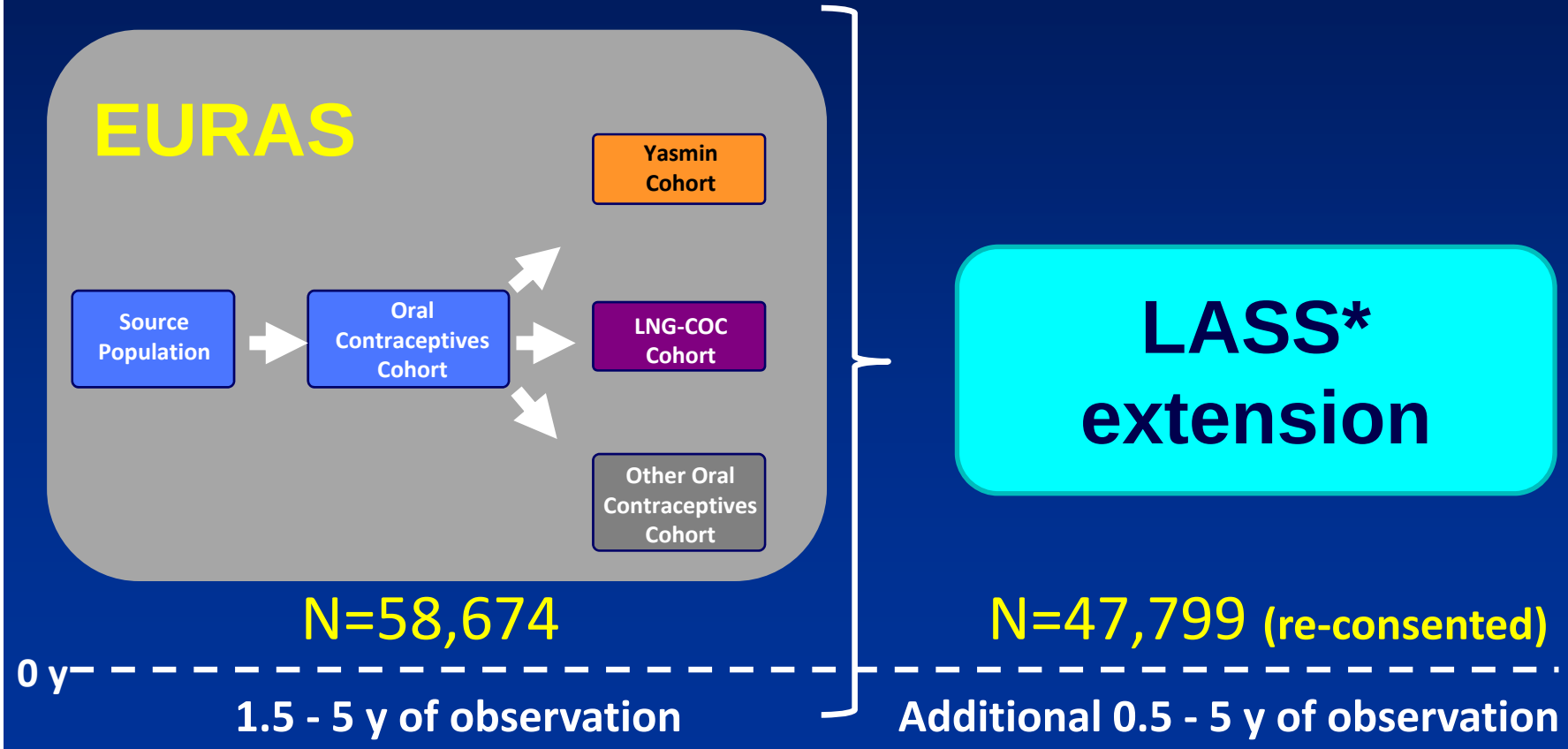


Yasmin: 26 events; Incidence rate 9.1 / 10,000 WY (95% CI: 5.9 – 13.3)
LNG: 25 events; Incidence rate 8.0 / 10,000 WY (95% CI: 5.2 – 11.7)
Other OCs: 52 events; Incidence rate 9.9 / 10,000 WY (95% CI: 7.4 – 13.0)

*Adjusted for age, BMI, duration of use, and personal and family history of VTE
As treated analysis

LASS: Study Design

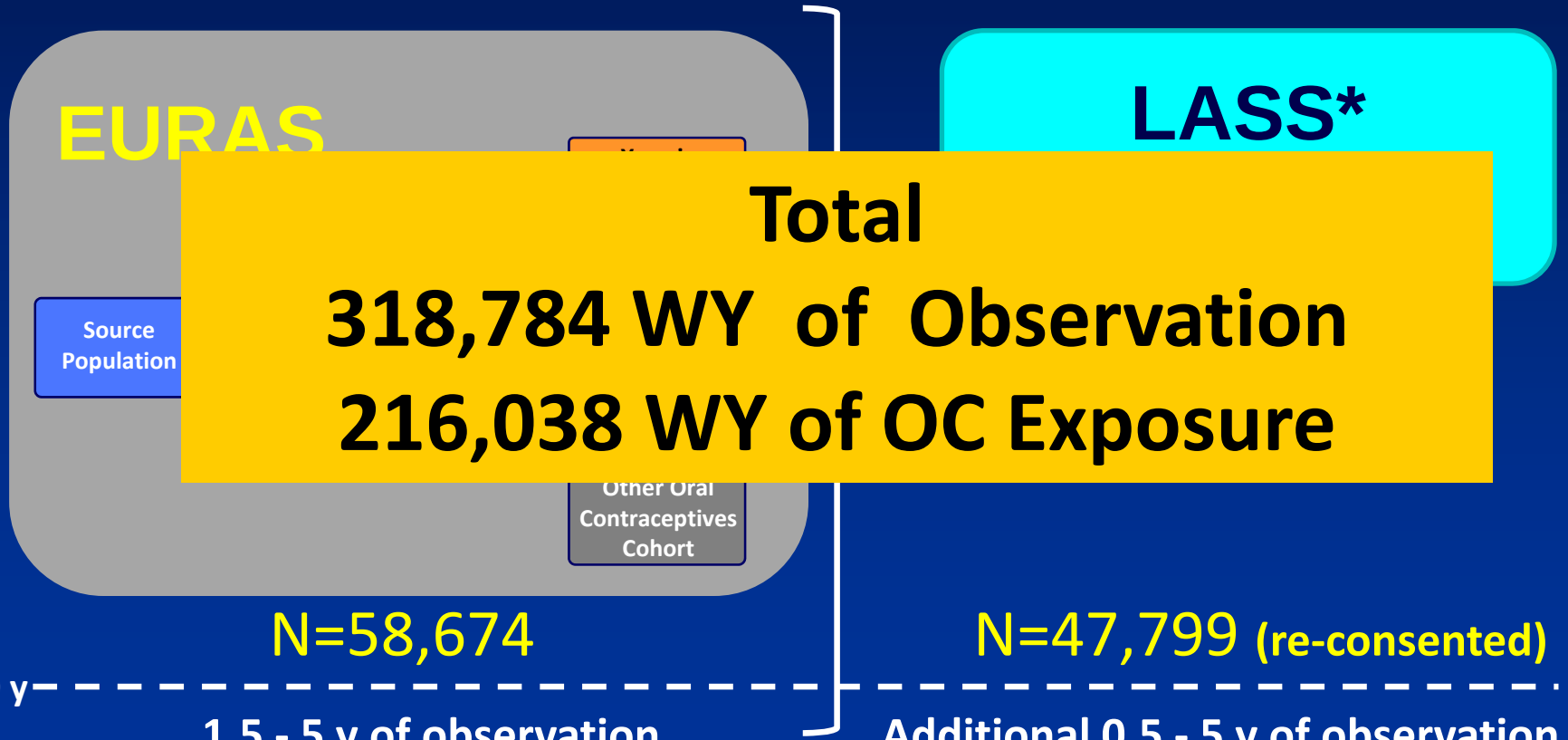
LASS RESULTS = EURAS+LASS extension



*ClinicalTrials.gov: NCT00676065

LASS: Study Design

LASS RESULTS = EURAS+LASS extension

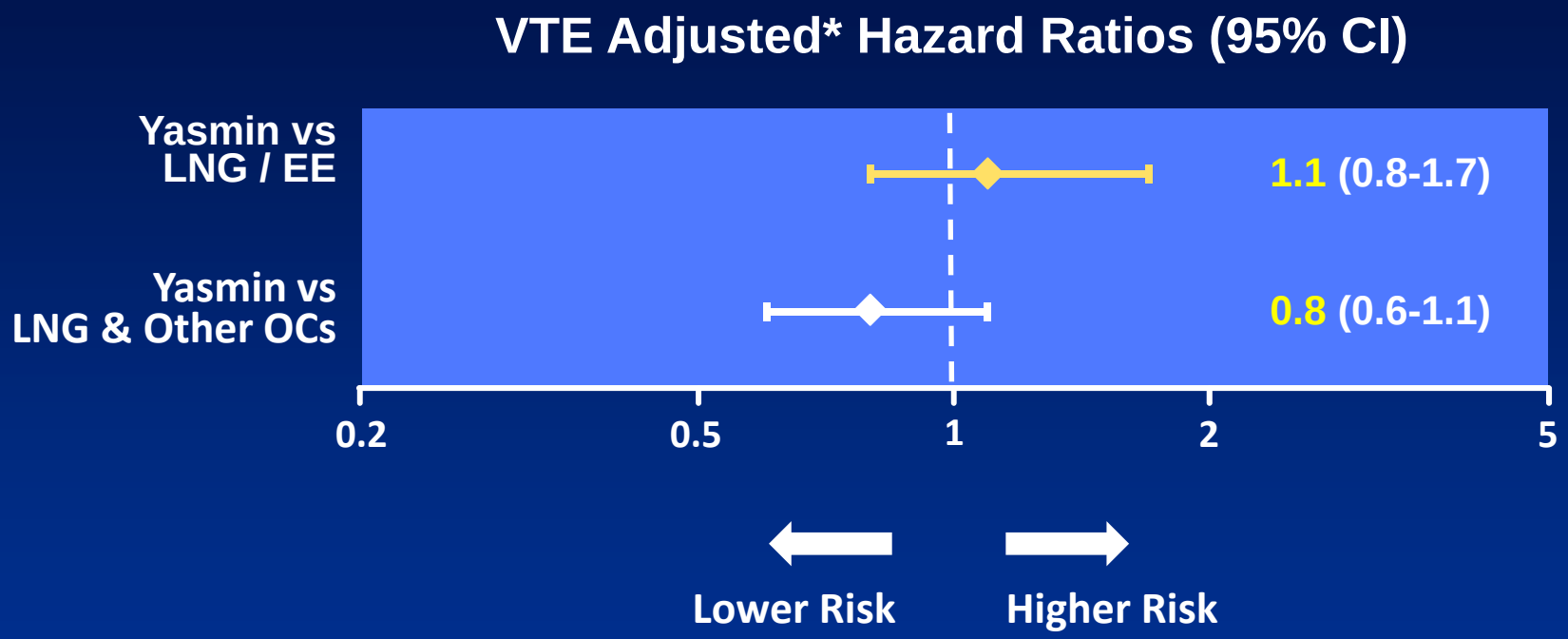


*ClinicalTrials.gov: NCT00676065

LASS Study: Strengths & Limitations

- Strengths
  - Community-based study with up to 10 years of follow-up
  - Adjusted for pre-defined confounding factors (including age, BMI, history of VTE); sub-analysis for duration and pattern of use, including first-time ever users
  - VTE cases confirmed by chart review and blinded adjudication
- Limitations
  - Events and exposure self-reported by subjects and may be influenced by memory
  - Active surveillance process with prompted recall
  - Inclusion in study required patient consent

LASS Study (EURAS + LASS): Risk of VTE



Yasmin: 56 events; Incidence rate 10.7 / 10,000 WY (95% CI: 8.1 – 13.9)
LNG: 53 events; Incidence rate 9.2 / 10,000 WY (95% CI: 6.9 – 12.0)
Other OCs: 144 events; Incidence rate 13.6 / 10,000 WY (95% CI: 11.4 – 16.0)

*Adjusted for age, BMI, duration of use, and personal and family history of VTE / As treated analysis

Dinger, Final Study report (September, 2011)

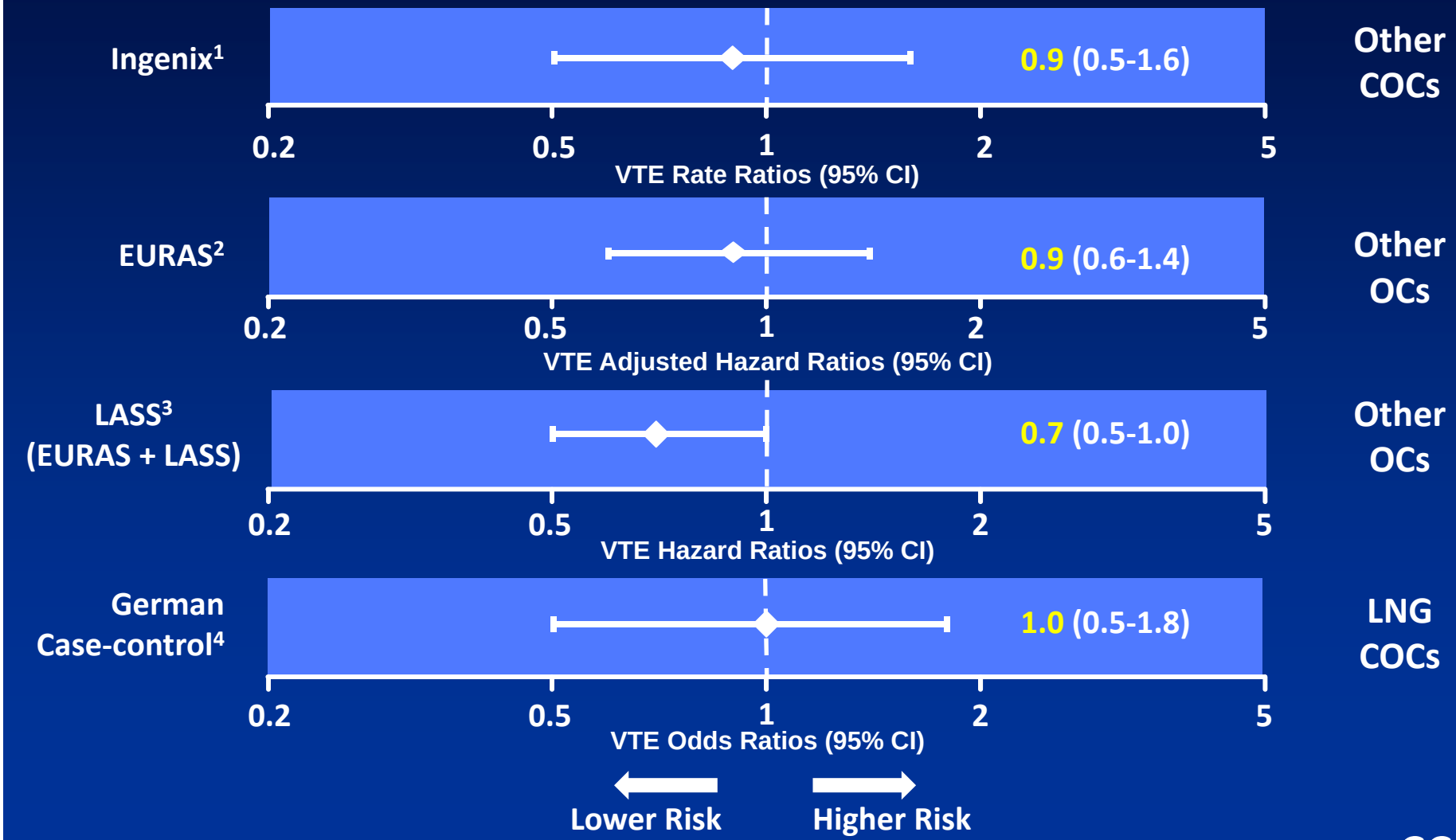
German Case-Control Study

- German community-based, case-control study
- N = 680 cases; N = 2,720 controls
  - Yasmin: N = 25 cases / 84 controls
  - LNG COC: N = 60 cases / 197 controls
- Outcome focused on risk of VTE only
  - Yasmin vs low-dose LNG COCs pre-specified secondary endpoint of study
- Adjusted† Odds Ratio: 1.0 (0.5-1.8)

†Adjusted for BMI, duration of use, personal and family history of VTE, parity, educational level, chronic disease, concomitant medication and smoking (as treated analysis)

Dinger J et al J Fam Plann Reprod Health Care 2010 ; 36 (3) 123-129

Yasmin Post-Approval Safety Studies: Results



1. Seeger et al 2007 2. Dinger et al 2007 3. LASS Final Study Report 2011 4. Dinger et al 2010

Post-Approval Safety Studies with Yasmin

Arterial Thromboembolic Events (ATE)

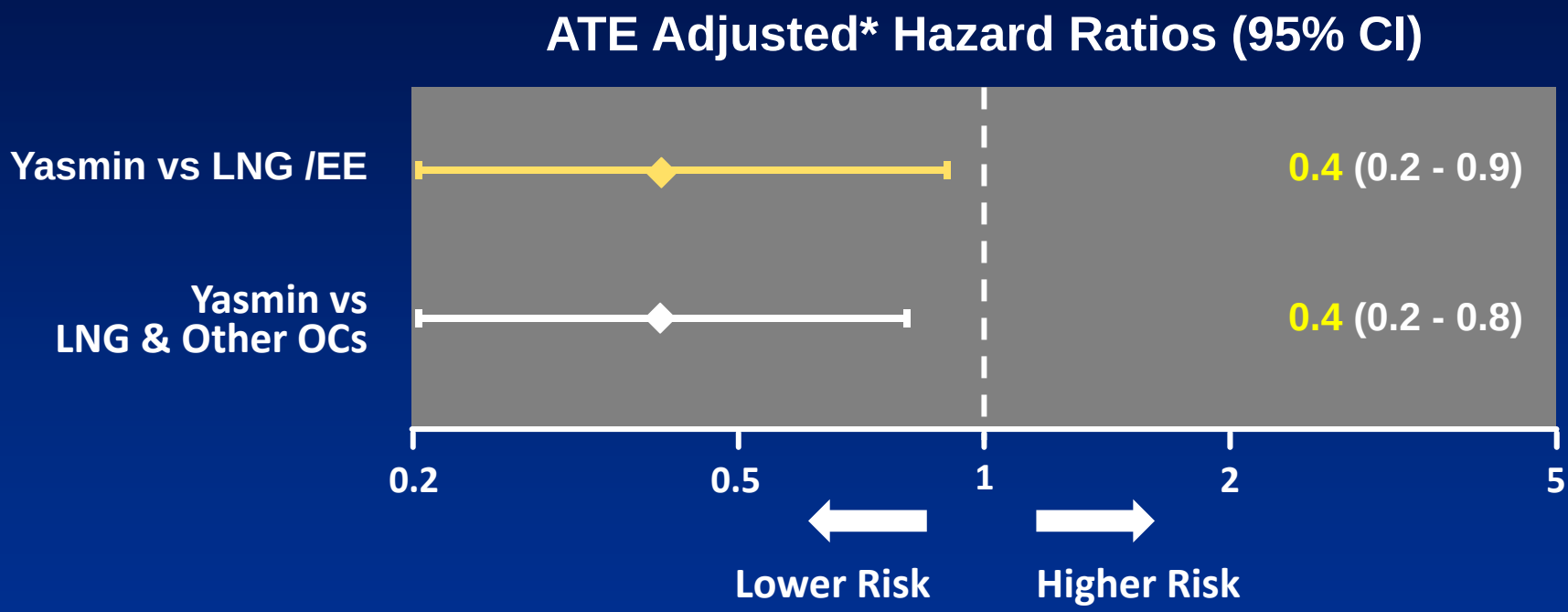
Post-Approval Safety Studies – Yasmin Arterial Thromboembolic Events as Outcome

Study	Type of Study	ATE as Pre-Defined Outcome
Ingenix	Prospective cohort	Yes (FDA)
European Active Surveillance Study (EURAS)	Prospective cohort	Yes (EMA)
Long-Term Active Surveillance Study (LASS)	Prospective cohort	Yes

LASS Study: Arterial Thromboembolic Events

- Recorded as serious adverse events (SAEs)
- Clinical chart review
- ATE defined as
  - Acute myocardial infarction (AMI)
  - Stroke
  - Transient ischemic attack (TIA)

LASS Study:
Risk of Arterial Thromboembolic Events



Yasmin: 7 events; Incidence rate 1.3 / 10,000 WY (95% CI: 0.5 – 2.8)
LNG: 22 events; Incidence rate 3.8 / 10,000 WY (95% CI: 2.4 – 5.8)
Other OCs: 34 events; Incidence rate 3.2 / 10,000 WY (95% CI: 2.2 – 4.5)

*Adjusted for age, BMI, smoking, hypertension, and family history of fatal ATE

Dinger, Final Study report (September, 2011)

Post-Approval Safety Studies with Yaz

Post-Approval Safety Studies with Yaz

Study	Type of Study	Post-Approval Commitment (Regulatory Authority)
International Active Surveillance Study (INAS)	Prospective cohort	Yes (FDA and EMA)

INAS-OC: Study design (Ongoing Study)

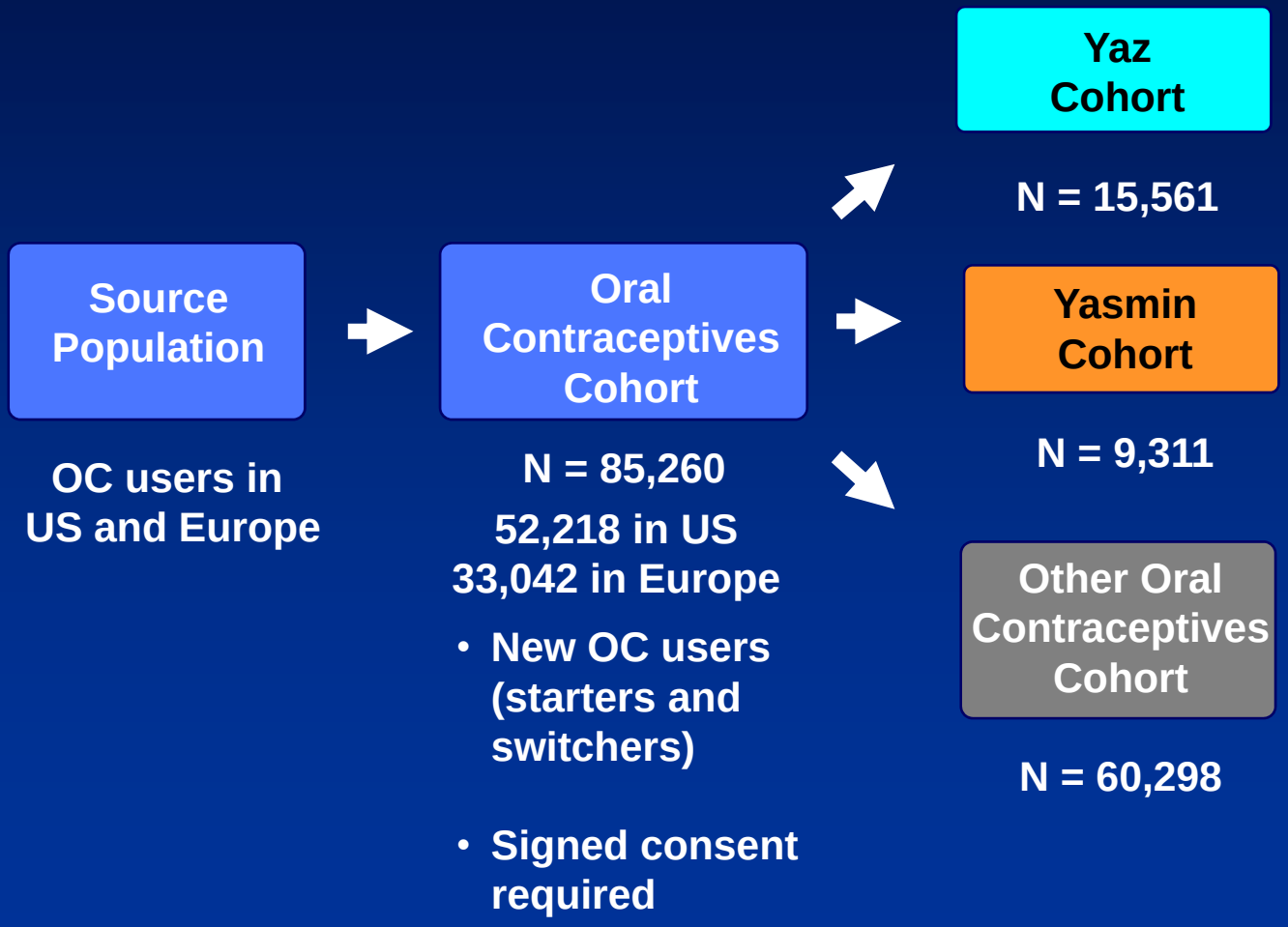
- US and European, prospective, noninterventional, controlled, cohort study
- N = 85,260 (Fully Enrolled); > 200,000 WY of observation expected

Primary Cohorts	USA		Europe	
(as of Feb 28/2011)	N	WY	N	WY
Yaz	10,303	16,014	5,258	3,632
Yasmin	3,893	7,164	5,418	4,248
Other OCs	37,932	60,952	22,366	17,607

- 2 – 5 years follow-up
- Several outcomes identified in protocol
  - VTE is focus of this presentation

ClinicalTrials.gov: NCT00335257

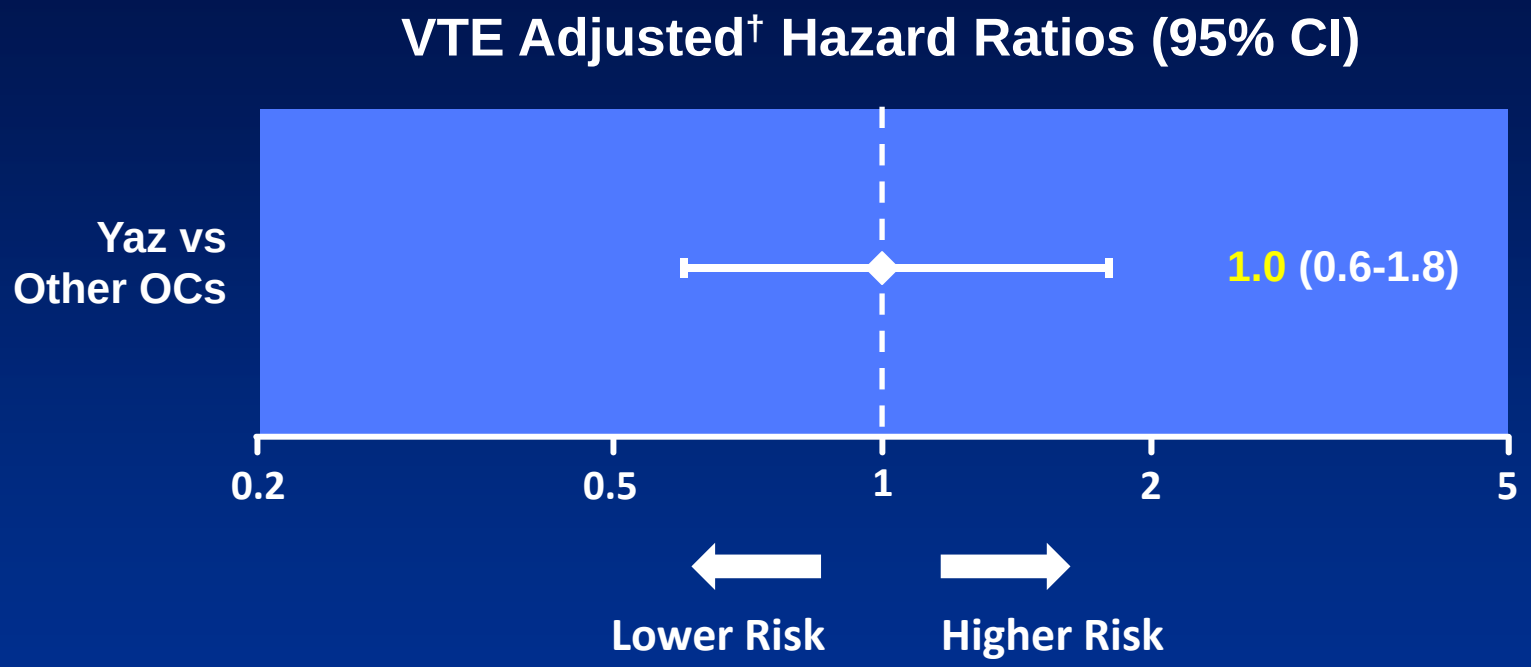
INAS-OC: Study Design



INAS Study: Strengths & Limitations

- Strengths
  - Community-based observational study in EU and US
  - Adjusted for pre-defined confounding factors (including age, BMI, history of VTE); sub-analysis for duration and pattern of use, including first-time ever users
  - VTE cases confirmed by chart review and blinded adjudication
- Limitations
  - Events self-reported by subjects and may be influenced by memory
  - Active surveillance process with prompted recall
  - Inclusion in study required patient consent

INAS: VTE Results (Interim*) – Hazard Ratio



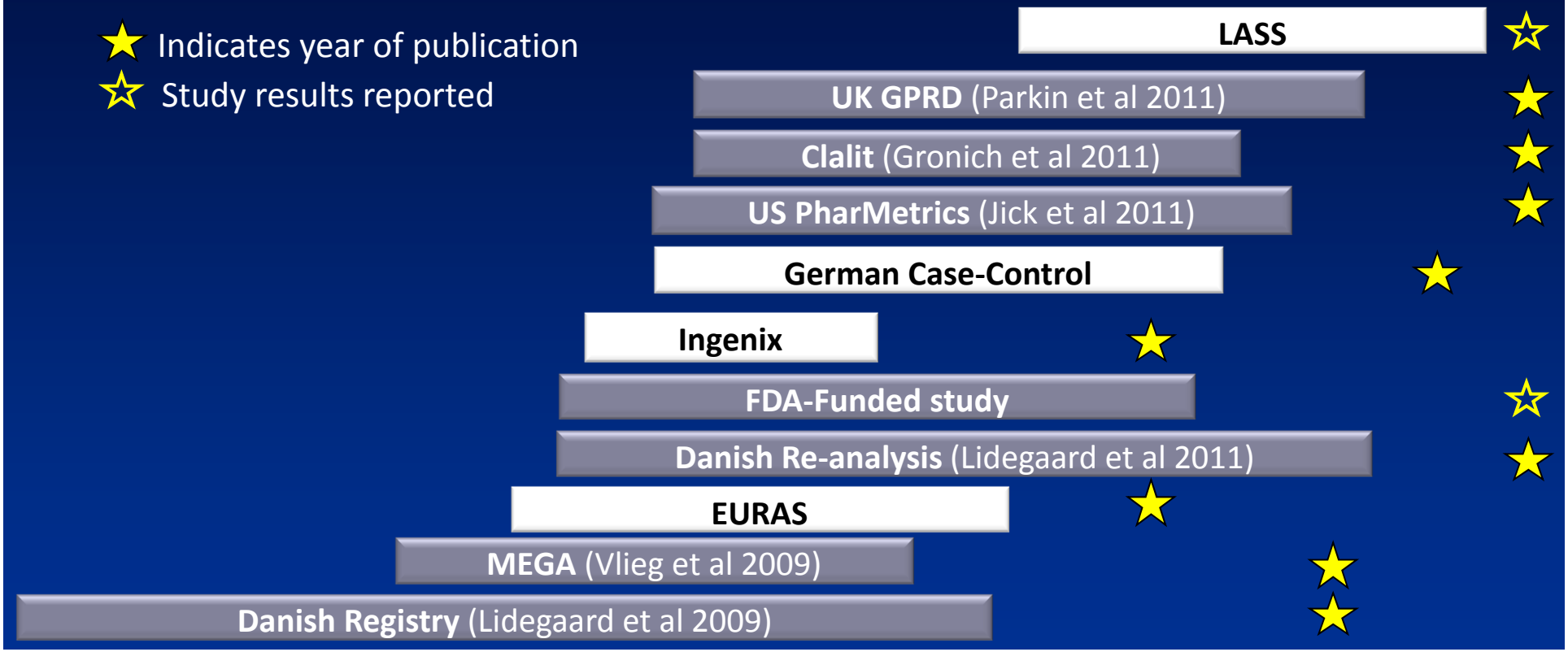
Yaz: 15 events; Incidence rate 7.6 / 10,000 WY (95% CI: 4.3 – 12.6)
Other OCs: 64 events; Incidence rate 8.1 / 10,000 WY (95% CI: 6.3 – 10.4)

† Adjusted age, BMI, duration and pattern of use, and personal and family history of VTE

*February 28th, 2011 data lock

Yasmin Studies:
Timeline of Studies and their Publication

★ Indicates year of publication
☆ Study results reported



1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011

APPROVAL DATES

US Yasmin

EU Yasmin

US Yaz

EU Yaz

US Beyaz

US Safyral

CC-41

Conclusions from Post-Approval Safety Studies

- Risk of VTE with Yasmin similar to other COCs studied
  - Ingenix
  - EURAS + LASS
  - German case-control study
- Risk of ATE with Yasmin similar to (or possibly lower than) other COCs studied
- Risk of VTE with Yaz (interim data) similar to other OCs studied
  - Interim data from the ongoing INAS study

Assessment of the Published Observational Studies

David A. Grimes, MD, FACOG,FACPM,FRCOG (Hon)
Distinguished Scientist, FHI 360

Clinical Professor, Department of OB/GYN
University of North Carolina School of Medicine
Chapel Hill, NC

Consultant Editor for Epidemiology
Obstetrics and Gynecology

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Disclosure

- Member of the INAS cohort study Data Safety Monitoring Board
- Paid for my participation in this Advisory Committee meeting

Objectives

- Describe a four-point checklist for evaluating observational studies
- Explore evidence for prescribing bias and differential misclassification
- Summarize the relationship between methodological rigor and study results for DRSP and VTE

A Four-point Checklist for Reading Observational Studies

Is there

1. Selection bias
2. Information bias
3. Confounding

Then….

4. Chance

Grimes DA, Schulz KF. Lancet 2002;359:248

Comparing VTE risk between COCs: Potential Biases

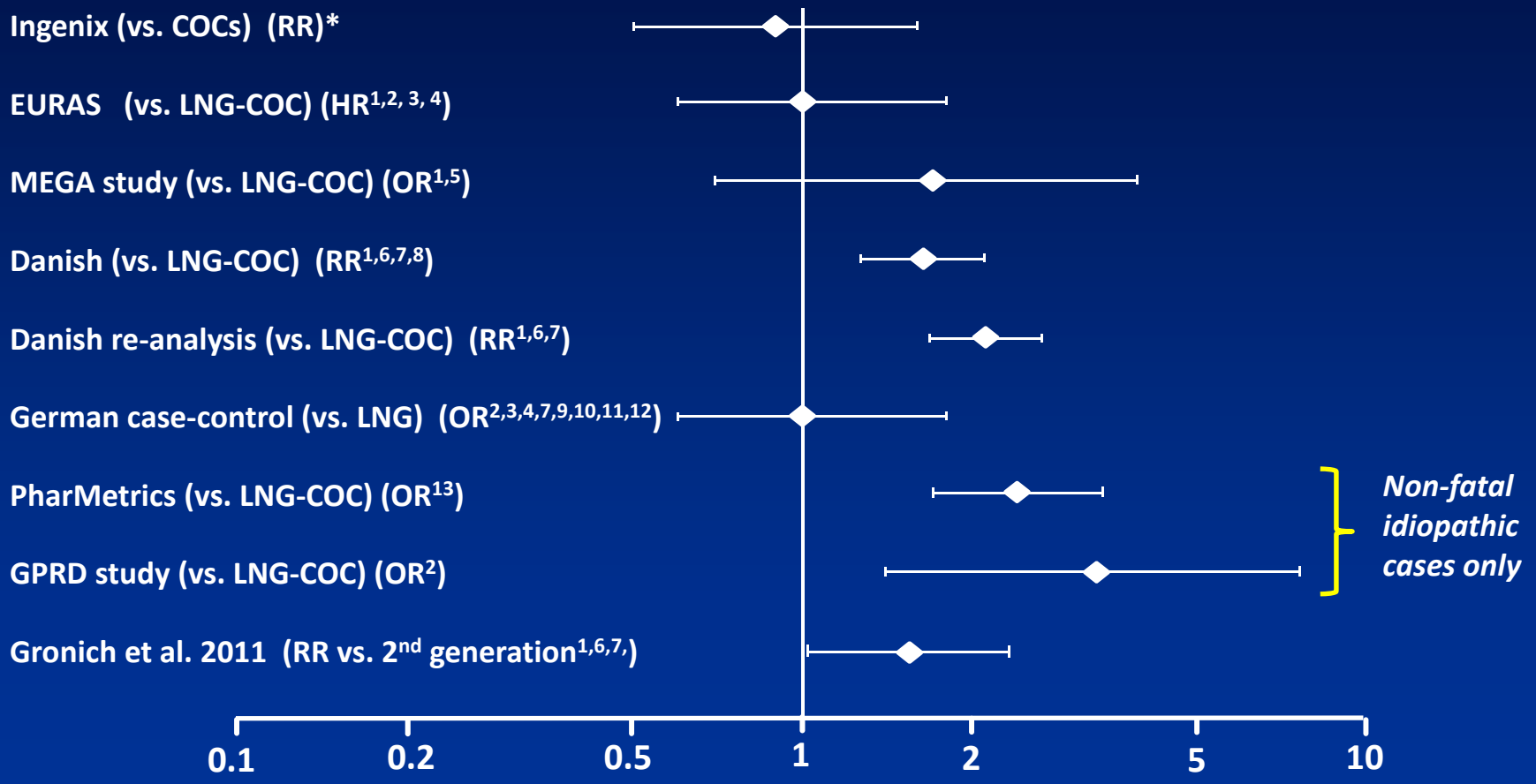
	Type of Bias
Duration of use / pattern of use	Selection
Attrition of susceptibles / healthy-user effect	Selection
Prescribing bias (channeling of higher-risk patients to new pill)	Selection
Validity of diagnosis for VTE (differential)	Information
Referral / diagnostic bias (differential)	Information

Shapiro and Dinger. J Fam Plann Reprod Health Care 2010;36:1
Heinemann and Heinemann. J Fam Plann Reprod Health Care 2011;37:132

Chronological List of Published Observational Studies on Yasmin and Risk of VTE

1. Dinger et al, 2007 (EURAS)
2. Seeger et al, 2007 (Ingenix)
3. Lidegaard et al, 2009 (Danish Registry)
4. van Hylckama Vlieg et al, 2009 (MEGA)
5. Dinger et al, 2010 (German Case-Control)
6. Jick et al, 2011 (PharMetrics)
7. Parkin et al, 2011 (GPRD)
8. Lidegaard et al, 2011 (“Re-analysis”)
9. Gronich et al, 2011 (Clalit)

VTE Risk With Yasmin Relative to Other OCs from Published Studies (adjusted risk)#



*comparator "Other COCs", incl. LNG-containing COCs; adjusted for current heavy smoking, hyperension, obesity and family history

#Adjusted for 1: age / 2: BMI / 3: duration of use / 4: VTE history / 5: period of inclusion / 6: calendar year / 7: education / 8: length of use / 9: parity / 10: chronic disease / 11: concomitant medication / 12: smoking / 13: duration of exposure / 14: site / 15: diabetes, hyperlipidemia, hypertension, cancer, smoking, obesity, duration of use

Limited Time Precludes a Detailed Discussion

Nine published studies, some large and complex

Five potential biases to consider in each

I will consider two general concerns:

- Prescribing bias (selection bias)
- Lack of VTE validation (information bias)

Prescribing Bias (Channeling)

Women at increased risk of VTE preferentially prescribed the newer DRSP pill

Empirical evidence:

1. **Obese women in EURAS study preferentially prescribed DRSP-containing COC***
2. **Obesity increases the risk of VTE**
3. **Result: confounding by indication****

*Dinger et al. Contraception 2007;75:344

**Shapiro and Dinger. J Fam Plann Reprod Health Care 2010;36:1

Calculation of Preference Ratio
Preference Ratio Used in Next 2 Slides

Given obesity,

- 60% of physicians prefer 3rd generation
- 30% of physicians prefer 2nd generation
- 10% of physicians have no preference

Then, the preference ratio (3rd/2nd) =
60%/30% = 2

Preference Ratios for Prescribing So-Called Third vs Second Generation Pills, Germany

Risk Scenario	Preference ratio (% third:% second)
Obesity	2
Smoking and obesity	3
Family history of DVT	3
First use of COC	3
Any combination of risk factors	4

Heinemann et al. Pharmacoepidemiology and Drug Safety 1996;5:285

Preference Ratios for Prescribing So-Called Third vs Second Generation Pills, England

Risk Scenario	Preference ratio (% third:% second)
Obesity	17
Smoking and obesity	27
Family history of DVT	23
First use of COC	15
Any combination of risks	59

Dunn et al. Pharmacoepidemiology and Drug Safety 1998;7:3

Support for Prescribing Bias Occurring

1. Empirical evidence

Dinger 2007 (EURAS study, Europe)

2. Physician surveys

- Heinemann 1996 (Germany)
- Dunn 1998 (England)
- Bitzer 2009 (Switzerland)

Heinemann et al. Pharmacoepidemiology and Drug Safety 1996;5:285
Dunn et al. Pharmacoepidemiology and Drug Safety 1998;7:3
Bitzer et al. Eur J Contracept Reprod Health Care 2009;14:258

Control of Potential Biases, Ingenix Study

- **Duration of use:** New users only (no COC use in prior 6 months)
- **Attrition of susceptibles:** Propensity score matching to ensure comparable cohorts
- **Prescribing bias:** Propensity score matching to ensure comparable cohorts
- **Validity of diagnosis for VTE:** Clinical chart review and adjudication by blinded reviewer
- **Referral/diagnostic bias:** Cannot be excluded

Control of Potential Biases, EURAS Study

- **Duration of use:** Analysis by groups based on duration of use / pattern of use
- **Attrition of susceptibles:** Analysis by groups based on history of prior use
- **Prescribing bias:** Potential confounding factors documented at baseline
- **Validity of diagnosis:** Clinical chart review and adjudication by blinded reviewers
- **Referral/diagnostic bias:** Cannot be excluded

Dinger et al 2010

- German case-control study
- Cases: Questionnaire and physician chart review
- Controls: Random sample from neighborhoods
- Blinded adjudication of VTE, control of personal and family confounding factors in analysis
- No increased risk for DRSP vs LNG pills

Dinger et al. J Fam Plann Reprod Health Care 2010;36:123

The Epidemic Intelligence Service at the CDC

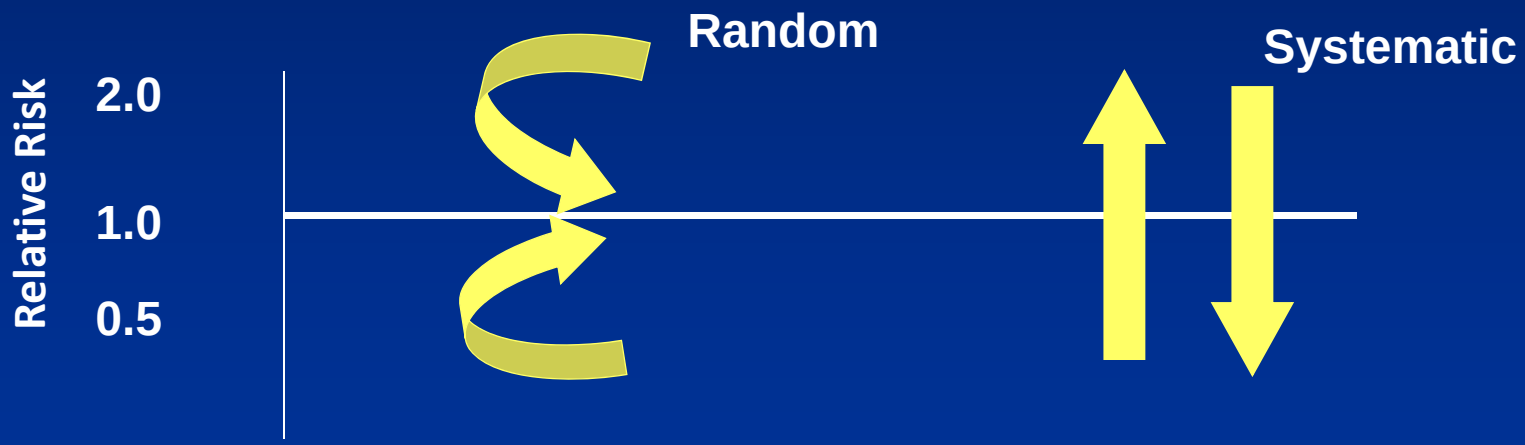
1. Confirm that the **exposure** occurred
2. Confirm that the **outcome** occurred

#1 generally well-done in published VTE studies

#2 often ignored

The Impact of Misclassification

- Random - Equal misclassification in cases and controls drives the RR estimate toward 1.0
- Nonrandom (Systematic) - Falsely elevates or lowers the RR estimate



RR = Relative Risk

Jick: The Need for Validation of Outcomes

"Unless one examines clinical records, it is **impossible** to ascertain whether a case of VTE has been documented by diagnostic tests (ie, whether it is in fact a case)…"

Jick et al. Lancet 1997;349:731

FDA Draft Guidance on Validation of Outcomes

"Because *electronic* administrative claims data are not collected for investigative purposes, but rather for patient care or reimbursement purposes, it is **vitally important** to ensure that medical outcomes of interest are validated (Lanes)."

FDA. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets. Draft guidance, February 2011, p. 17

Lidegaard on Outcome "Validation"

"We have the opportunity to link the discharge diagnoses…with those who were anticoagulated after the diagnosis, thus validating [sic] each case from this simple merger of data."

Lidegaard. Obstet Gynecol 2011;117:410, in response to Grimes. Obstet Gynecol 2010;116:1018

Wrong VTE Diagnoses in Danish Administrative Database, Patients 50-64 Years Old

1100 medical records examined

626 confirmed VTE

17 probable VTE

5 no relevant information

452 VTE ruled out

41% of reported VTE incorrectly coded

(25% on ward, 69% in emergency department)

Severinsen. J Clin Epidemiol 2010;63:223

Post-script to Lidegaard 2009

ELSEVIER

Journal of Clinical Epidemiology 63 (2010) 223–228

Journal of Clinical Epidemiology

Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution

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Accepted 30 March 2009

Post-script to Lidegaard 2009

Lidegaard re-analysis[1]: Audit of 200 randomly selected VTE cases in the Danish registry: 26% of ward-diagnosed cases not VTE, contrary to his prior claim of "10% misclassification"

Similar to 25% documented by Severinsen et al. 2010[2]

1. Lidegaard et al. BMJ 2011;343:d6423
2. Severinsen. J Clin Epidemiol 2010;63:223

Persistent Flaw in Lidegaard 2011 Reanalysis

- Women who could not have started DRSP COC before 2001

compared to

- Women who could have started LNG COC in 1994 or earlier

Analysis of first-ever users, Yasmin vs. LNG COCs:
RR 1.2 (95% CI 0.6-2.5)

Lidegaard final study report, Table 10

Observational Studies on Yasmin and Risk of VTE by Validation of VTE Cases

	Appropriate Validation	Risk of VTE
Dinger et al, 2007 (EURAS)	Yes	Similar
Seeger et al, 2007 (Ingenix)	Yes	Similar
Lidegaard et al, 2009 (Danish Registry) Lidegaard et al, 2011 (Re-analysis)	No	Increased
van Hylckama Vlieg et al, 2009 (MEGA)	Yes	Increased (non-significant)
Dinger et al, 2010 (German Case-Control)	Yes	Similar
Jick et al, 2011 (PharMetrics)	No	Increased
Parkin et al, 2011 (GPRD)	No	Increased
Gronich et al, 2011 (Clalit)	No	Increased

Differential Information Bias in VTE Studies

Referral bias

News media: women with symptoms more likely to seek care

Diagnostic bias

News/professional media: women using suspect product more likely to have diagnostic evaluation

What drives these biases?

Medical Journals, among others…

Dutch GPs warned against new contraceptive pill

Tony Sheldon *Utrecht*

Dutch GPs are being advised by their own professional body not to prescribe a new low dose, monophasic oral contraceptive, marketed under the trade name Yasmin, until studies have established whether it is as safe as other contraceptive pills.

lack of epidemiological data on the risk of thrombosis from Yasmin.

The Dutch Medicines Evaluation Agency, which has a leading role in the European Union in

Sheldon. BMJ 2002;324:869

MEGA Case-Control Study (van Hylckama Vlieg et al, 2009)

- Improper control group*
- Controls not chosen independent of known risk factors: 41% of controls were spouses of VTE cases in the MEGA database
- Failure to control for potential confounding factors identified in earlier reports from MEGA
- Odds Ratio for VTE with DRSP vs LNG: 1.7 (0.7-3.9)

(no statistically significant increase in risk)

*Grimes DA, Schulz KF. Lancet 2005, 365:1429-33

Unresolved Issues

Lidegaard, 2009, 2011 (Danish Registry)	Extensive misclassification of VTE; inadequate control of potential confounding
Van Hylckama Vlieg, 2009 (MEGA)	Improper control group; inadequate control of potential confounding
Jick, 2011 (PharMetrics)	Lack of case validation; purging of non-idiopathic cases
Parkin, 2011 (GPRD)	Same as above; gross undercount of DVT (more PE than DVT)
Gronich, 2011 (Clalit)	Lack of VTE validation; incomplete control of potential confounding factors

Risk of VTE with Yasmin: Best Available Evidence

Author	Study type	Risk
Dinger 2007	Prospective cohort	Similar ₸
Seeger 2007	Database	Similar*
Dinger 2010	Case-control	Similar*

₸ Yasmin vs all other COCs, including LNG-containing COCs
* Yasmin vs LNG oral contraceptives

Conclusions

- The literature on VTE risk with DRSP-COCs is inconsistent, but this is explained by the varied study designs and inadequate control of bias
- Prescribing bias (channeling) and information bias readily account for reported weak associations
- More recent studies did not compare “like to like”
- Studies with more rigorous methods show no greater risk of VTE with DRSP-COCs than other COCs

Review and Remarks: FDA-Funded Study First Phase

Robert Makuch, PhD

Professor, Biostatistics
Yale University School of Medicine

Disclosures

Paid Consultant, Bayer Healthcare Pharmaceuticals

No vested interest in meeting outcome

Objectives

- Brief remarks regarding the FDA funded (Kaiser, Medicaid) study first phase
- Assess this study in terms of its design, conduct, analysis, and interpretation
- Describe its limitations and strengths
- Conclusions

Combined Hormonal Contraceptives (CHCs): Risk Assessment of Cardiovascular Disease

- Study objective: “To determine prevalence and incidence rates for ATE and VTE events and all-cause and cause-specific mortality in women exposed to 3 newer hormonal contraceptives compared to older frequently prescribed low estrogen hormonal contraceptives”
- Access dates: July 2000 through December 2007
- Four sites

CHC Groups

Yasmin

- Yasmin (30 mcg EE)

COMP Group

- Combination of LNG, NETA, NGM
- 20 to 35 mcg of EE included (30% of subjects on COCs contain 20 mcg EE)

LNG2 Group

- 30 mcg EE/LNG only
- Subset of COMP group

LNG = Levonorgestrel
NETA = Norethindrone acetate
NGM = Norgestimate

Endpoints

- **Venous Thromboembolism (VTE)**
  - Inpatient
  - Outpatient
- **Arterial Thromboembolism (ATE)**
  - Acute myocardial infarction (AMI)
  - Ischemic stroke
- **Mortality**
  - All cause
  - CVD mortality

Guides to Assessing the FDA-Funded Study

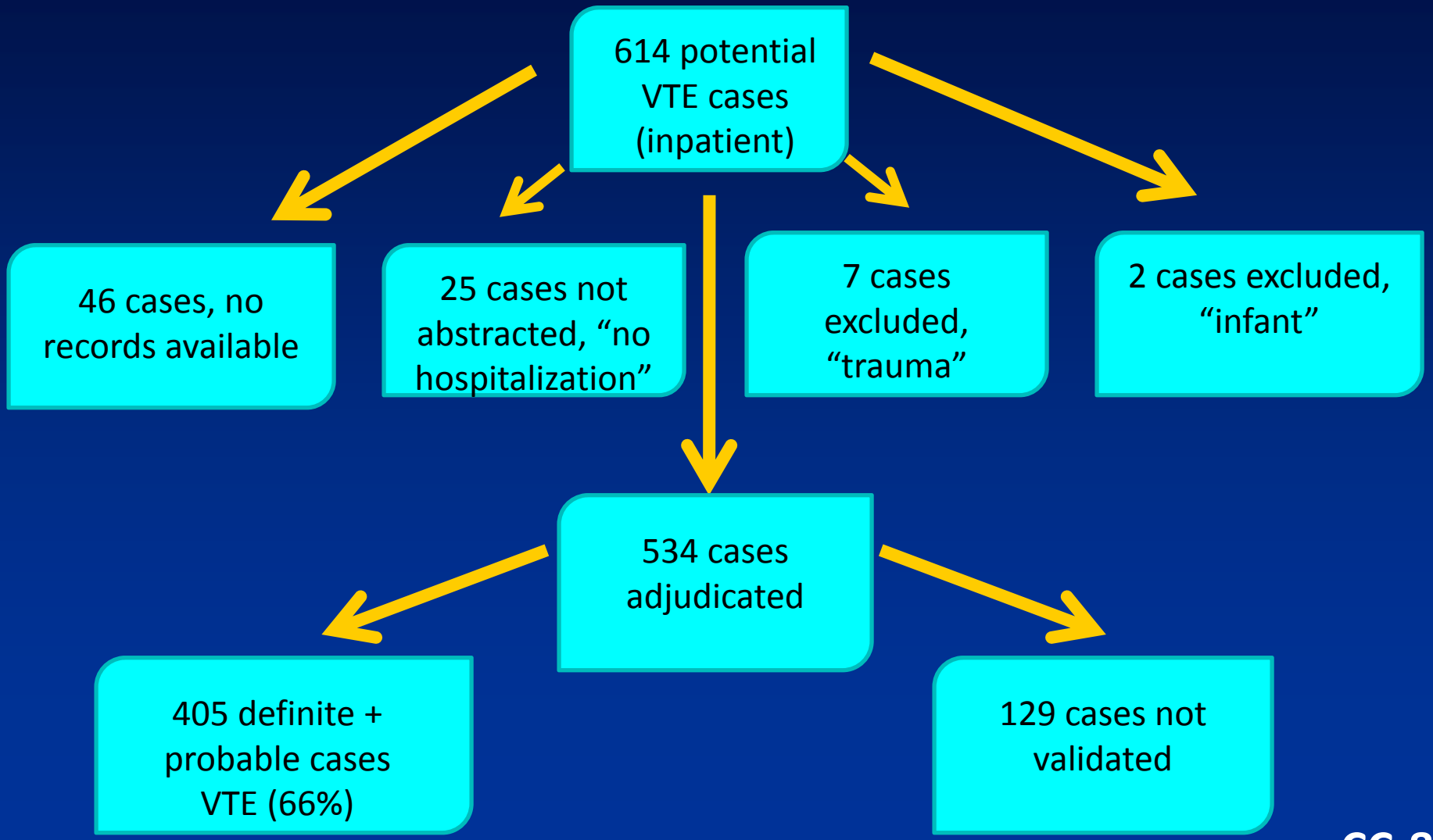
- Guidance for Industry and FDA Staff – Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (Draft Guidance, FDA, 2011)
- Guidelines for Good Pharmacoepidemiologic Practices (GPP) (Pharmacoepidemiology and Drug Safety, 2008)

Designing a Study

- "A scientifically valid study protocol should be developed…by predefining certain elements related to the design, analysis, conduct, and reporting…**All of the elements described within this guidance should be addressed in the protocol."***
- GPP highlights several critical factors including: "Providing a written protocol, with dated amendments and justifications."*
- No protocol provided until December 7, 2011

* Pages 4-5, Draft Guidance, FDA, 2011

Validation Process for Inpatient VTE Among CHC Users



Endpoint Validation: Additional Remarks

- Outpatient VTEs validated at only 1 of 4 study sites
- Stroke: Of 241 potential cases, 186 adjudicated, 78 verified (32% validated for analysis)
  - 11 cases no hospitalization, 11 no endpoint, 19 no records available, 9 trauma, 5 infants
- AMI: Of 92 potential cases, 72 adjudicated, 60 validated (65% validated for analysis)
  - 11 cases no hospitalization, 1 no endpoint, 8 records unavailable
- "Because electronic administrative claims data are not collected for investigative purposes…it is vitally important…that medical outcomes of interest are validated."

*** Page 17, Draft Guidance, FDA, 2011**

The Data: Confounders

- Key confounders
  - Not measured
  - Poorly measured
  - Missing data
- Examples include:
  - Personal history of VTE
  - BMI
  - No distinction between first-ever users vs repeat users in "new users" group
  - Family history of VTE
  - Smoking (for ATEs)

The Data: Some Additional Remarks

- Many covariates required coding for at least 2 outpatient visits or one hospitalization code.*
- Limited coding
- "Prevalence of most covariates was low, with most occurring in fewer than 1% of women."*
- Prevalence of polycystic ovarian syndrome (PCOS) was 0.02%*, while it is estimated that PCOS is present in 5–10% of reproductive-age women (up to 70% of whom are obese)†

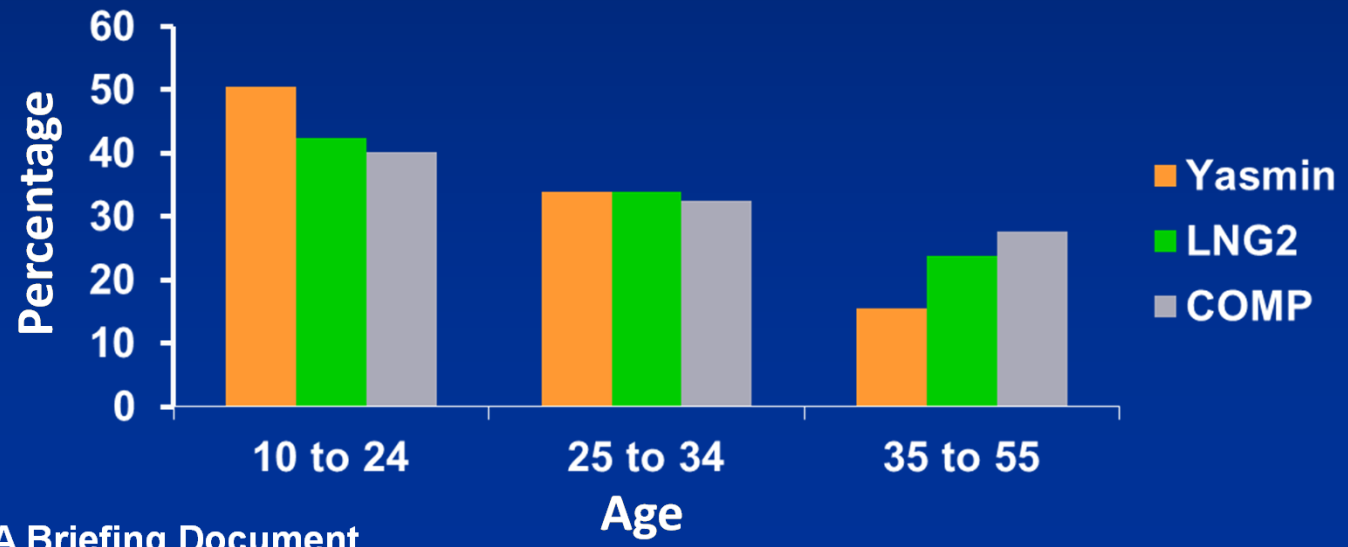
* FDA-funded study page 25

†Beyond infertility: Polycystic Ovary Syndrome (PCOS) US Dept. HHS, NICHD, April, 2008

Design Issues

- Comparator drug group “COMP” included several contraceptive products with multiple EE doses (30% 20 mcg), as opposed to original single dose selection*
- Preferential prescribing based on age, with Yasmin users younger than COMP or LNG. Younger users more likely to be first time ever users

Age at Initiation of COC, Kaiser sites, New Users†



* Page 20 FDA Briefing Document

† Derived from table 4b2 FDA-funded study

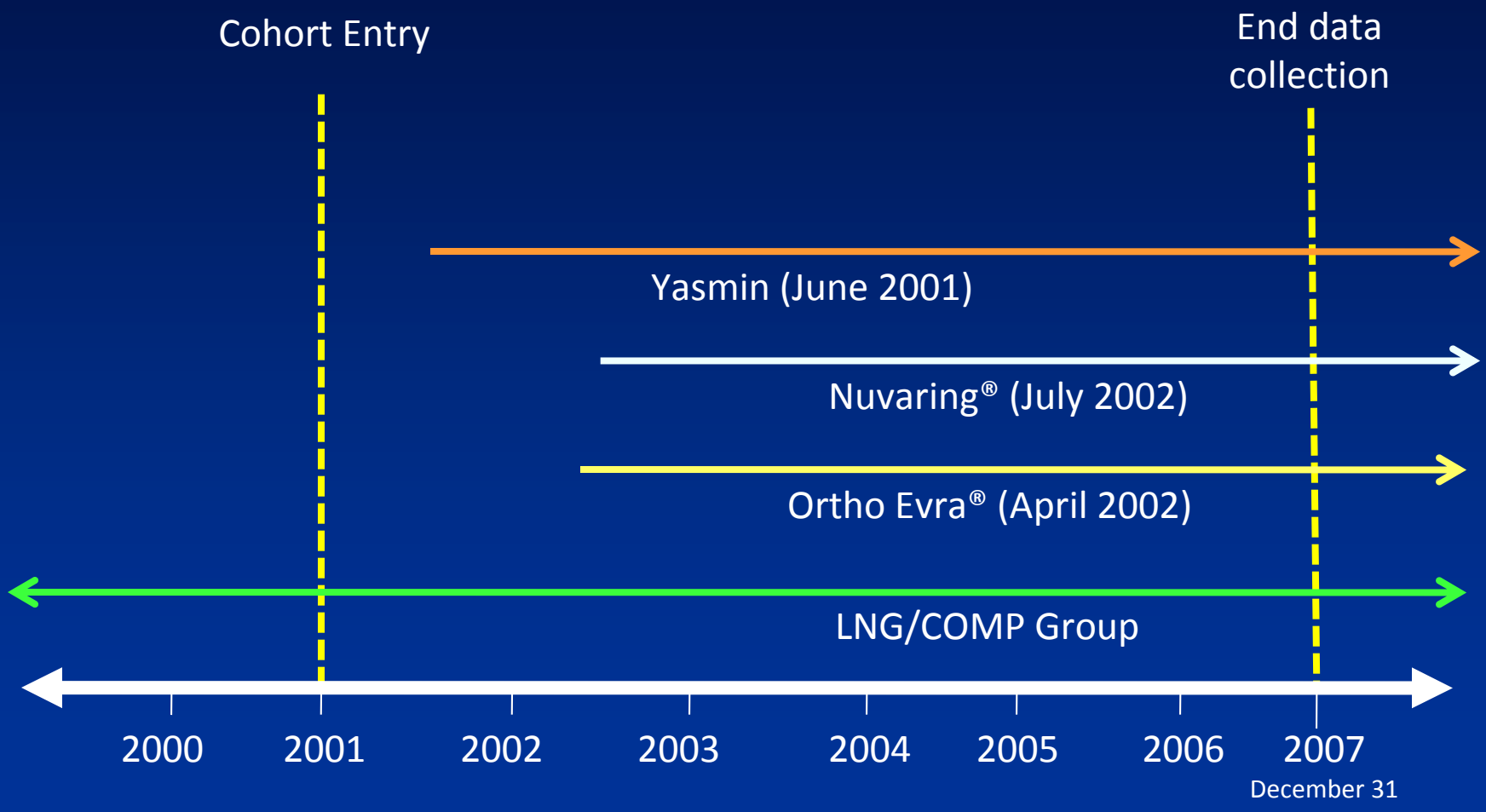
VTE Rate per 10,000 WY, all Users

	# of cases	IR* (unadjusted†)	IR* (adjusted)
Yasmin	144	7.6/10,000 WY	10.2/10,000 WY
LNG2	161	6.6/10,000 WY	6.6/10,000 WY
COMP	389	6.3/10,000 WY	6.0/10,000 WY

***Adjusted for age, site**

† Unadjusted IR calculated from the FDA-funded study phase 1
IR = Incidence rate

Year of Introduction to Market of CHCs Studied in the FDA-funded Study



Analysis Remarks

- No protocol provided until December 7, 2011
- Analytical Issue: Compare 'like to like' is preferred and mimics RCTs
  - First time users to first time users
  - Repeat users to repeat users
  - Switchers to switchers
  - Short term duration to short term duration
- Propensity score method allows direct examination of 'like to like', and how well the subjects are matched to one another
- Propensity score "has been used increasingly to address confounding"*
- Proportional hazards regression is complex, and masks ability to examine 'like to like' comparisons
- No diagnostics presented to support proportional hazards model

* Page 13, Draft Guidance, FDA, 2011

Hazard Ratio of VTE: Yasmin vs COMP by Duration of Use in New Users

Duration of Use (months)*

	<3	3-6	6-12	>12
Yasmin	**1.93 (1.24 - 3.00)**	1.14 (0.59 - 2.21)	**2.80 (1.48 - 5.29)**	1.32 (0.68 - 2.56)

*Data from table 13b1, FDA-funded study

Analyses for ATE: Multiple Comparisons (Yasmin vs LNG2)

- Analysis all users - nonsignificant
- Analysis Kaiser only - nonsignificant
- Analysis Medicaid only - nonsignficant
- Analysis older users - nonsignificant
- Analysis younger users - nonsignificant
- Analysis new users only - nonsignificant
- Analysis Kaiser only, new only - significant
- Analysis Medicaid only, new only - nonsignficant
- Analysis older users, new only - significant
- Analysis younger users, new only - nonsignificant

Strengths of First Phase of the FDA-Funded Study

- Large population size and number of events; community-based "real-world" data
- Provided a "New User" cohort (although unable to distinguish first time users)
- Linked records to state mortality files; able to capture fatalities
- Evaluated two different US populations
- Acknowledgment of second phase, currently under consideration, that would include more extensive medical record review/data acquisition of important but missing confounders*

* Page 41, FDA-Funded Study

Overall Conclusions: FDA Funded Study First Phase

- Key endpoint adjudication incomplete
- Confounders not measured/poorly measured/missing data
- Comparator drug group “COMP” included several contraceptive products with multiple EE doses (30% 20 mcg), as opposed to original single dose selection. Yasmin was 30 mcg only
- No direct confirmation of “like to like” in the analysis. Further support needed to justify adequacy of proportional hazards regression model
- Non-overlap of available information among CHC groups in year 2001

A Clinician's Perspective

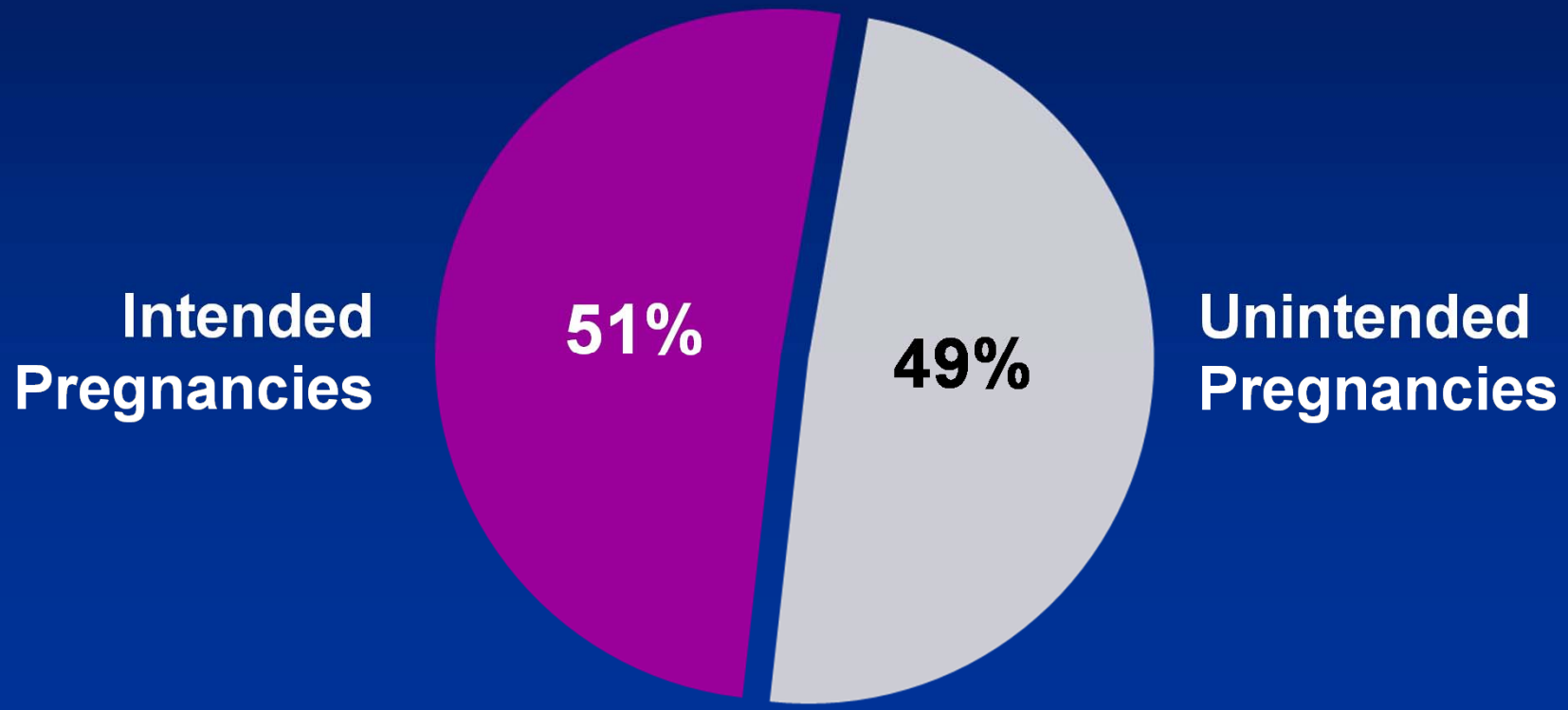
Andrea S. Lukes, MD, MHSc, FACOG
ObGyn Physician
Women's Wellness Clinic
Carolina Women's Research and Wellness Center
Durham, NC

Outline

- Contraception
- Why drospirenone containing pills appeal to women and their clinicians
- Clinician's perspective on risk of VTE
- Summary

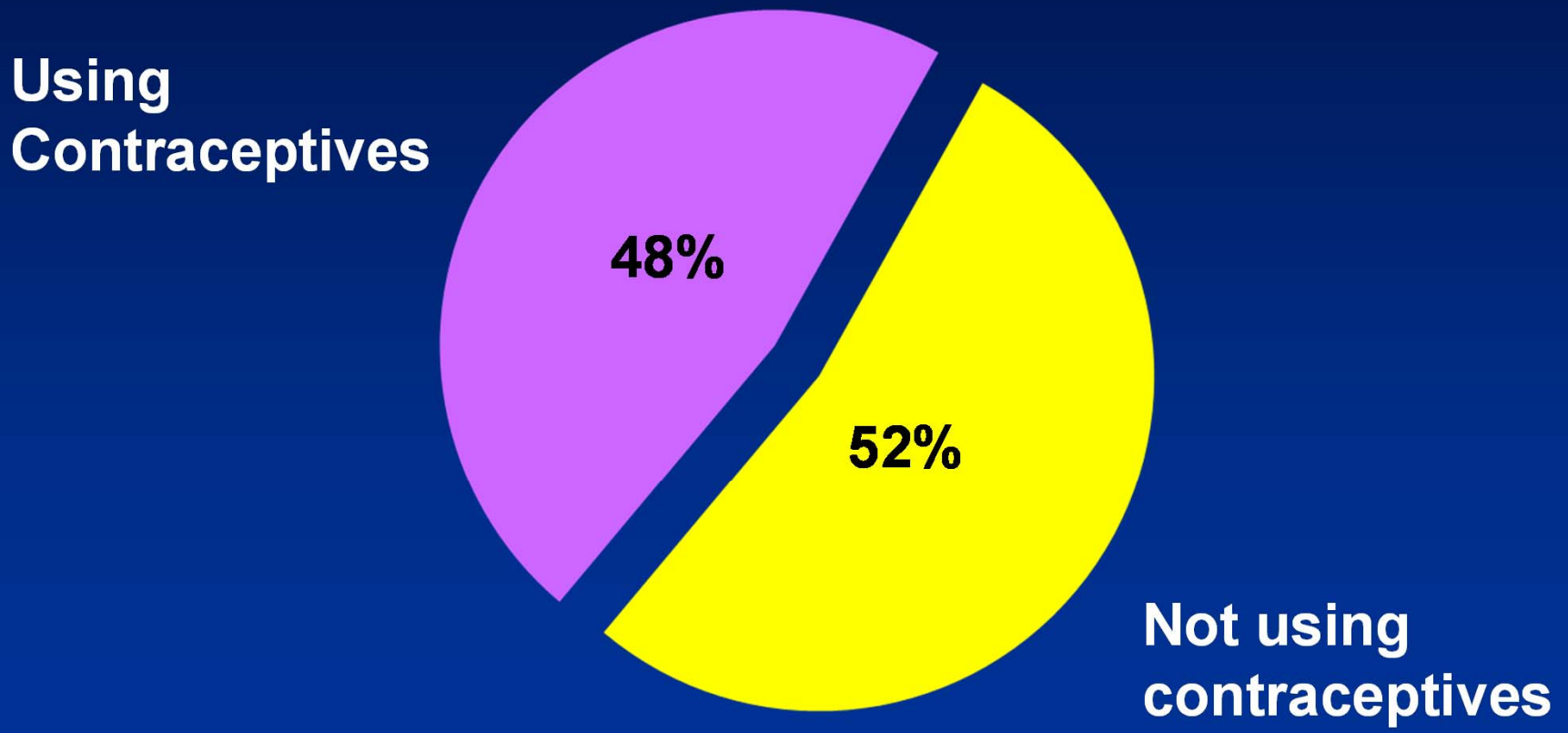
Contraception in the US

- Important aspect of women's healthcare
  - Unintended pregnancy rates remain high



Finer et al. Contraception 2011 84 ; 478-485

Women Reporting An Unintended Pregnancy: US



Finer et al. Perspect Sex Reprod. Health. 2006; 38 (2) 90-96

Contraception: Combined Oral Contraceptives (COCs)

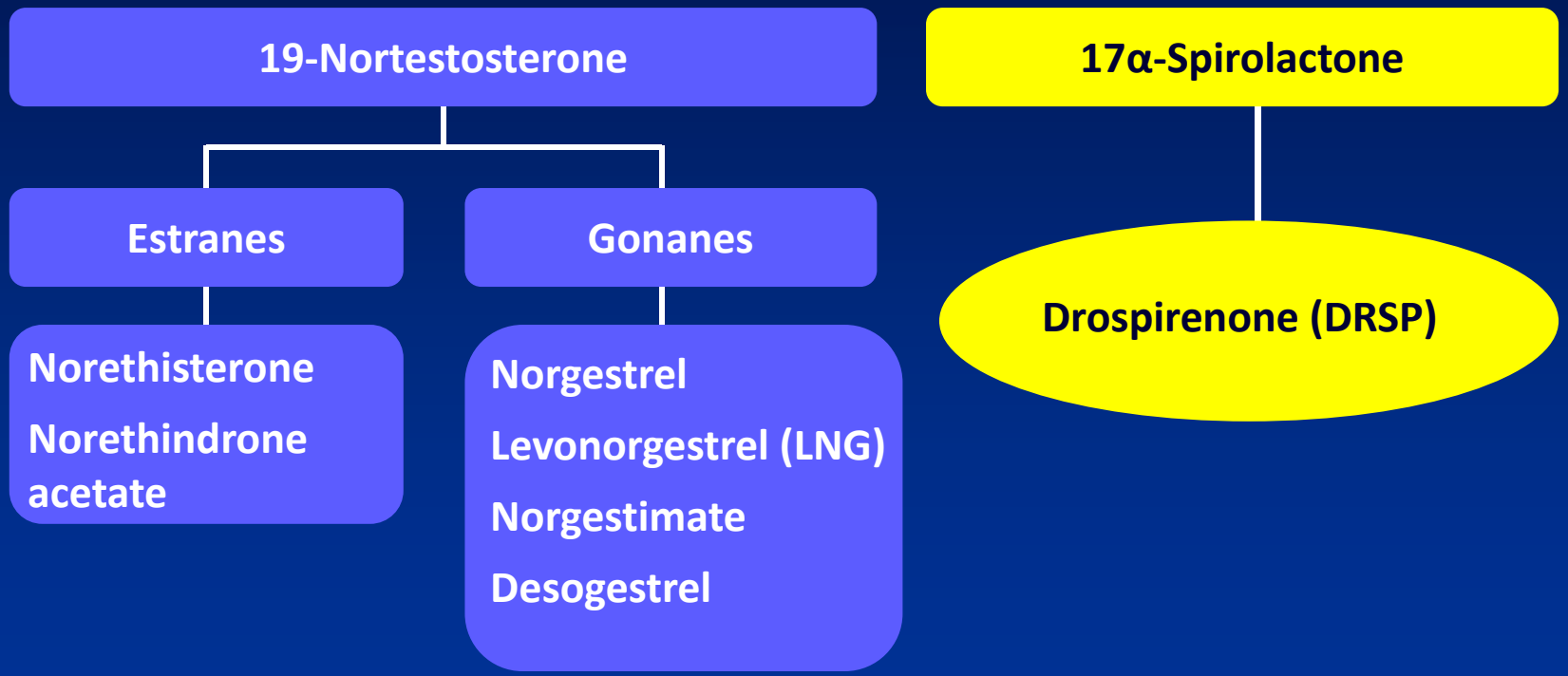
- 50 years of use within the US
- Within the US (2006-2008 data): COCs are the leading method of contraception[1]
- Risks of VTEs in COC users are significantly influenced by a woman's own risk factors
- COCs are NOT all the same

[1] http://www.cdc.gov/nchs/data/series/sr_23/sr23_029.pdf

CHOICE: COCs are not all the same . . . AND women are not all the same

- Choice of Regimens
  - 21/7 or 24/4 or Extended
- Estrogen dose varies
  - Doses (mg): 0.01, 0.02, 0.03 . . . . all EE ≤0.05 mg
- Type of progestin varies….

Progestins in Oral Contraceptives



Mishell DR, Jr. *Comprehensive Gynecology,* 5th ed. St. Louis, MO: Mosby; 2007:275-325.
Oelkers W. *Mol Cell Endocrinol.* 2004;217:255-261.
Stanczyk FZ. *Rev Endocr Metab Disord.* 2002;3:211-224.

Reasons for Discontinuation of COCs

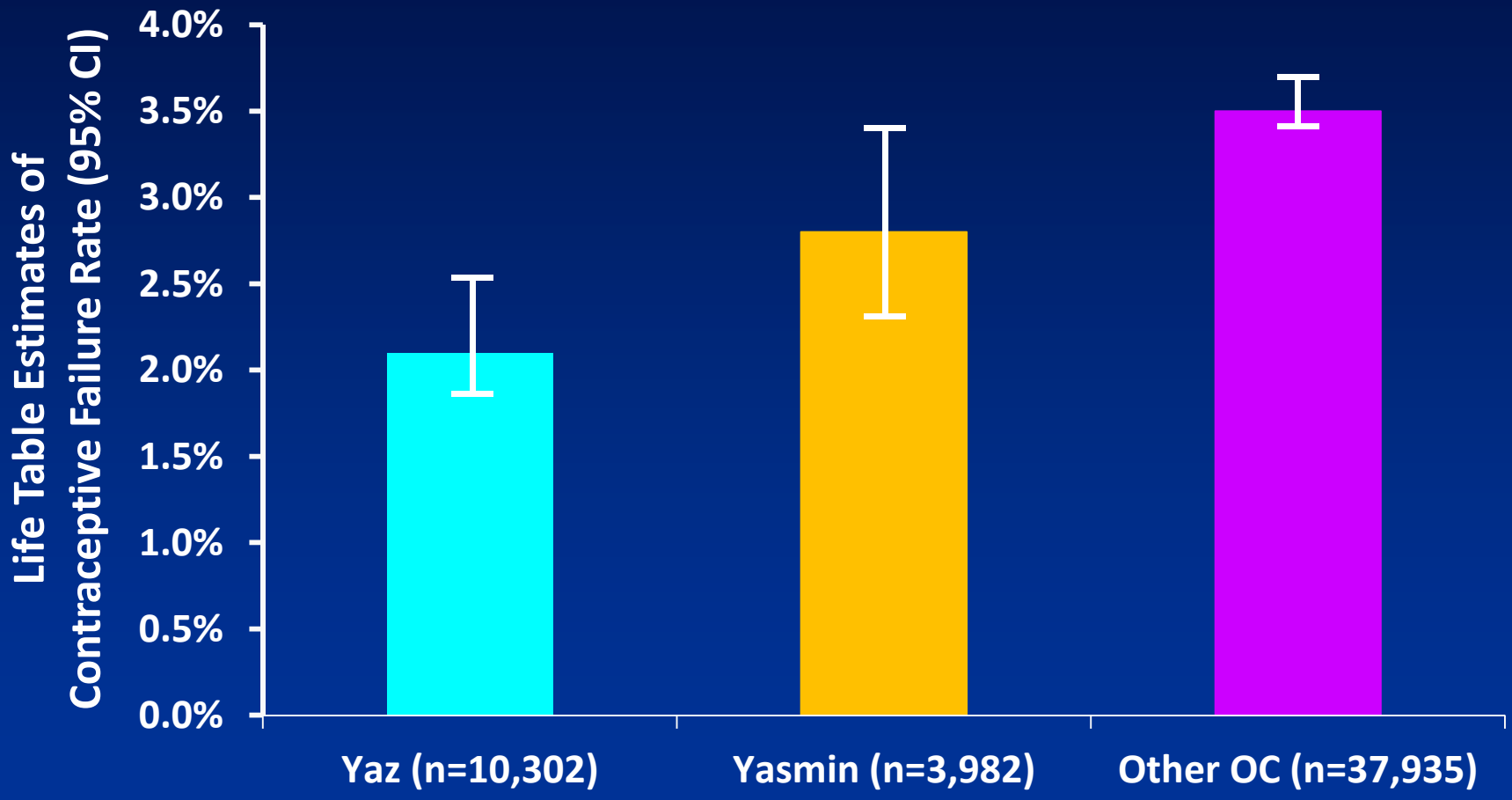
- The most common reason for discontinuing oral contraception is poor tolerability
- Common tolerability issues associated with discontinuation include:
  - Headaches
  - Weight gain
  - Breast tenderness
  - Bleeding irregularities
  - Mood changes
  - Nausea

Rosenberg MJ and Waugh MS. Am J Obstet Gynecol 1998; 179:577-82

Why Do DRSP-COCs Appeal to Women/Clinicians?

- Effective contraception
- Additional DRSP properties
  - Anti-mineralocorticoid
  - Anti-androgenic
- Secondary indications of newer DRSP-COCs
  - Moderate acne (Beyaz, Yaz)
  - PMDD (Beyaz, Yaz)
  - Folate supplementation (Beyaz, Safyral)

INAS Efficacy Analysis: Contraceptive Failure Rates*

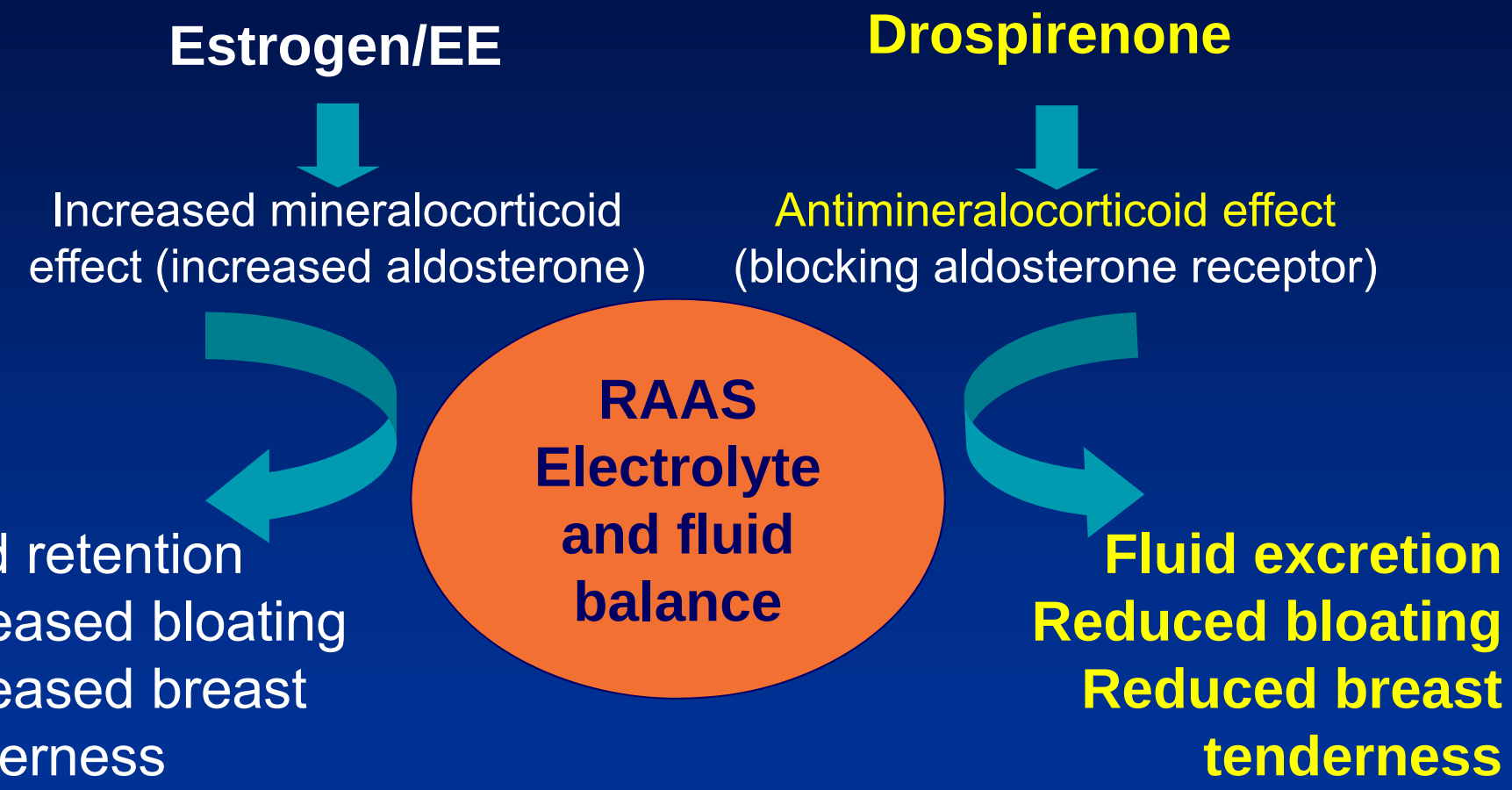


* Life table estimates of contraceptive failure after one year

Dinger et al. *Obstet Gynecol* 2011;117(1):33-40

CC-104

Renin-Angiotensin-Aldosterone System (RAAS): Effect of Combined EE and DRSP

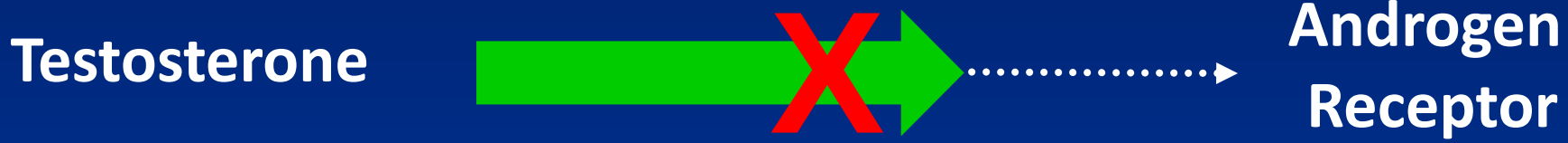


Halbreich U and Monacelli E. Primary Psychiatry 2004;11(12):33-40
Krattenmacher R. Contraception 2000;62:29-38
Oelkers WKH. Steroids 1996;61:166-71

Drospirenone: Anti-Androgenic Effects

Drospirenone

Anti-Androgenic effect
(blocking testosterone receptor)



↓ Acne
↓ Hirsutism
↓ Seborrhea

Halbreich U and Monacelli E. Primary Psychiatry 2004;11(12):33-40; Krattenmacher R. Contraception 2000;62:29-38; Oelkers WKH. Steroids 1996;61:166-71

Why DRSP COCs?

- Effective contraception
- Generally well tolerated
- Secondary indications (Yaz, Beyaz, Safyral)

Counseling on the Key Risks of Venous Thrombosis for COC Users

Previous VTE[1]

Increasing age[1]

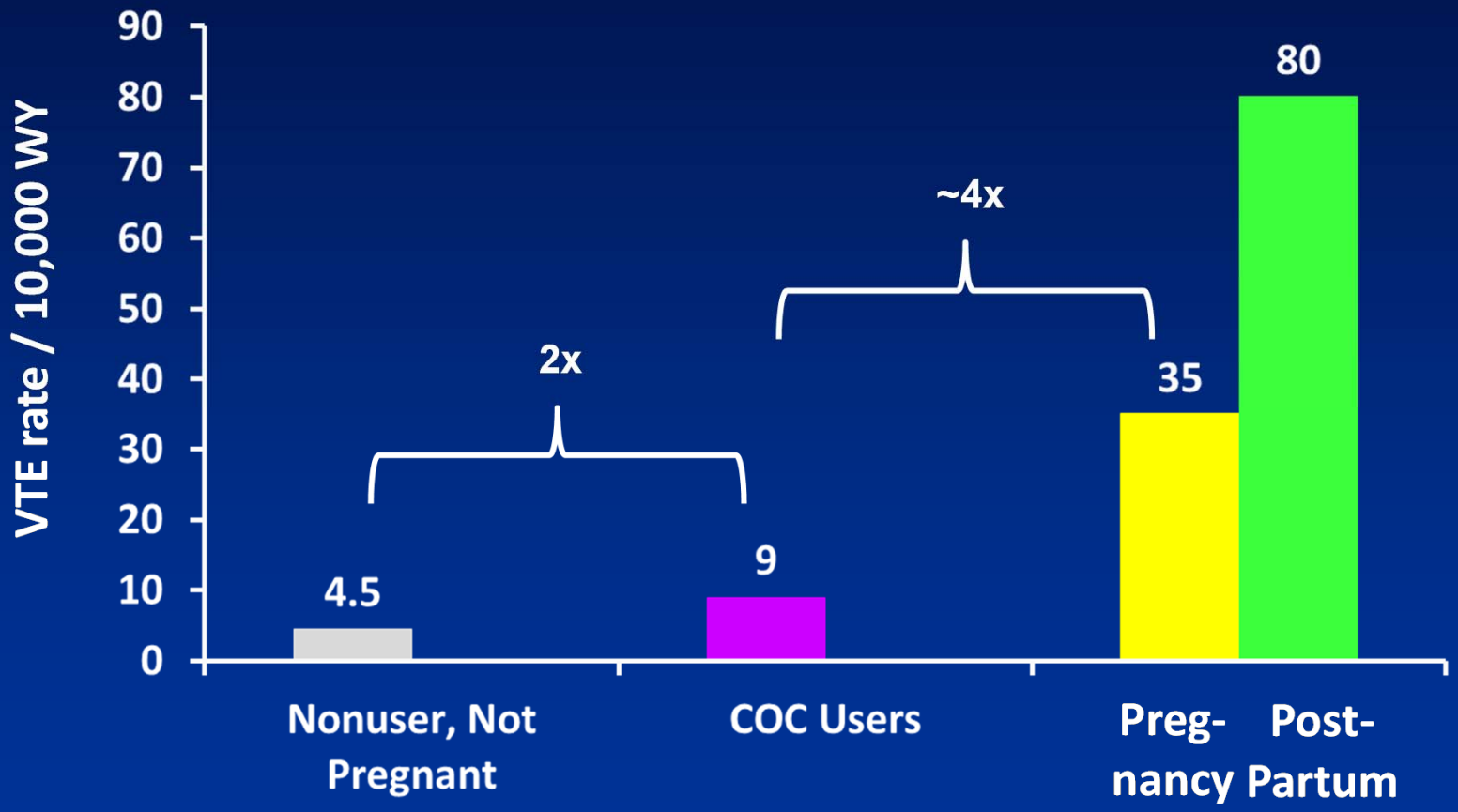
Prolonged immobility[1]

Inherited and acquired hematological conditions[1]

Body Mass Index (BMI)

1 Anderson FA, Spencer FA, Risk Factors for Venous Thromboembolism, Circulation, 2003, 107:I-9-I-16

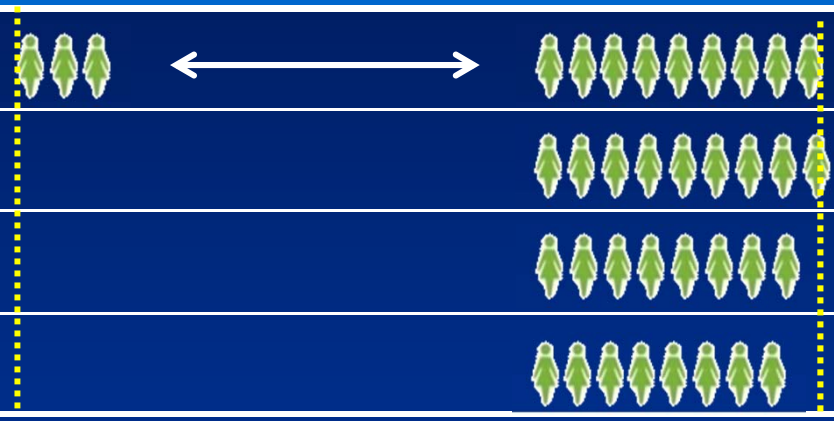
VTE Rates in Reproductive Age Women



Adapted from Heinemann and Dinger, Drug Safety 2004; 24(13):1001-1018

Risk of VTE Across Recently Published Studies, the FDA study and USPI (crude rates per 10,000 WY)

Source (per 10,000WY)	
US Package Insert (3 to 9)	
Lidegaard 2011 (9.3)	
Jick 2011[#] (7.9)	
FDA study (7.6)	



3 per 10,000 WY **9 per 10,000 WY**

[#] extrapolated to idiopathic + non-idiopathic

CC-110

Conclusions

- DRSP-COCs play an important and unique role for contraception
- Risks of VTEs in COC users are significantly influenced by a woman's own risk factors
- The current package insert adequately reflects the information I need to counsel my patients on the risk of VTEs with DRSP-COCs

Final Comments

Leo Plouffe Jr, MD

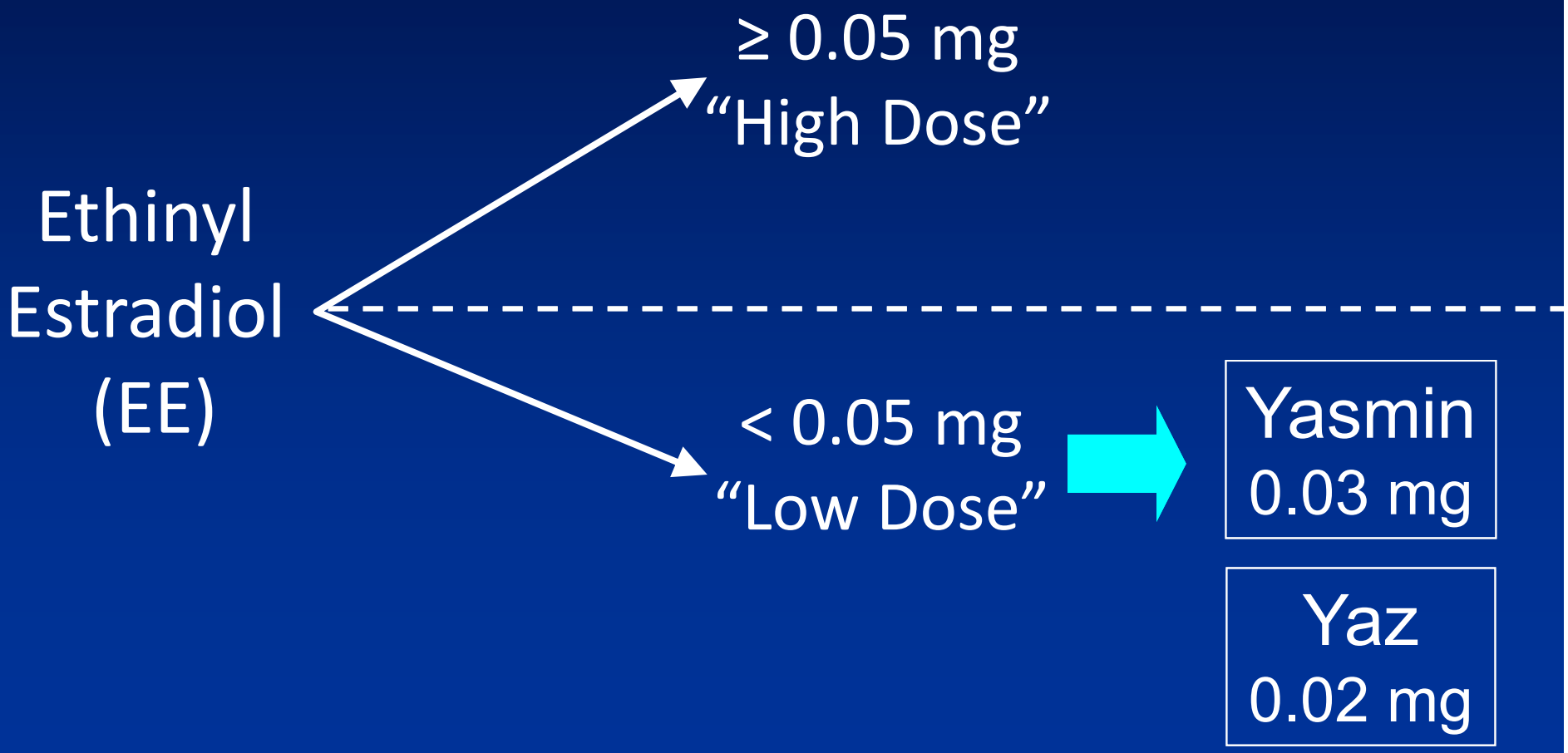
Vice President, US Medical Affairs
Women's HealthCare
Bayer HealthCare Pharmaceuticals, Inc.

DRSP-COCs

	Yasmin (Safyral*)	YAZ (Beyaz*)
Ethinyl Estradiol	0.03 mg	0.02 mg
Drospirenone	3 mg	3 mg
Dosing Regimen	21 days active 7 days placebo	24 days active 4 days placebo
Indications	1. Prevention of Pregnancy	1. Prevention of Pregnancy 2. (1) + PMDD 3. (1) + Moderate Acne
Contraindications Warnings and Precautions	– – – – – – – – – – Consistent – – – – – – – – – –	

* Includes levomefolate calcium 0.451mg to increase serum folate levels

Combination Oral Contraceptive: Estrogen Component



Comparison of Drospirenone with Other Progestins

	Progestogenic activity	Androgenic activity	Antiandrogenic activity	Antimineralo-corticoid activity
Progesterone	+	–	(+)	+
Drospirenone	+	–	+	+
Desogestrel	+	(+)	–	–
Levonorgestrel	+	(+)	–	–
Norgestimate	+	(+)	–	–
Norethisterone	+	+	–	–

+ relevant activity; **(+)** activity not clinically relevant; **–** no activity

Krattenmacher R. *Contraception*. 2000;62:29–38;
Schindler AE, *et al. Maturitas*. 2003;46(Suppl 1):S7–16

YAZ Compared to Yasmin

	Yasmin	YAZ
Ethinyl Estradiol	0.03 mg	0.02 mg
Drospirenone	3 mg	3 mg
Dosing Regimen	21 days active 7 days placebo	24 days active 4 days placebo
Indications	1. Prevention of Pregnancy	1. Prevention of Pregnancy 2. (1) + PMDD 3. (1) + Moderate Acne
Contraindications Warnings and Precautions	– – – – – – – – – Consistent – – – – – – – – –	

CC-116

INAS Efficacy Analysis: Life-table Estimates of Contraceptive Failure for 24-day and 21-day Regimens of DRSP vs Other OCs

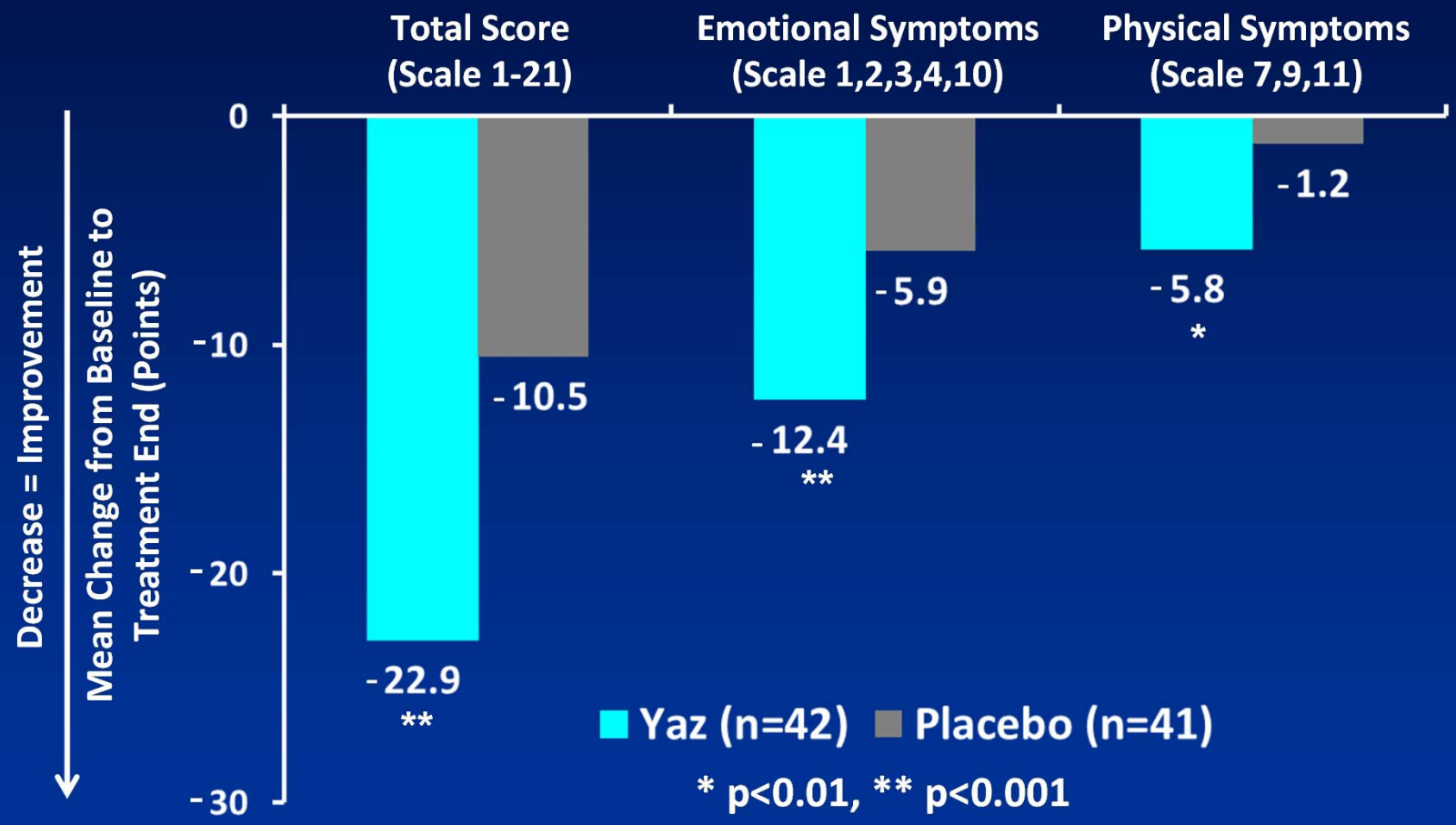
Life-Table Estimates of the **Rate of Contraceptive Failure** After Oral Contraceptive Use

	1 yr	2 yr	3 yr
Yaz	2.1 (1.7-2.4)	3.4 (2.9-4.0)	4.7 (3.8-5.6)
Yasmin	2.8 (2.2-3.3)	4.5 (3.6-5.4)	5.7 (4.5-6.9)
Other OC	3.5 (3.3-3.7)	5.4 (5.1-5.7)	6.7 (6.2-7.1)

Point estimates (95% confidence intervals)

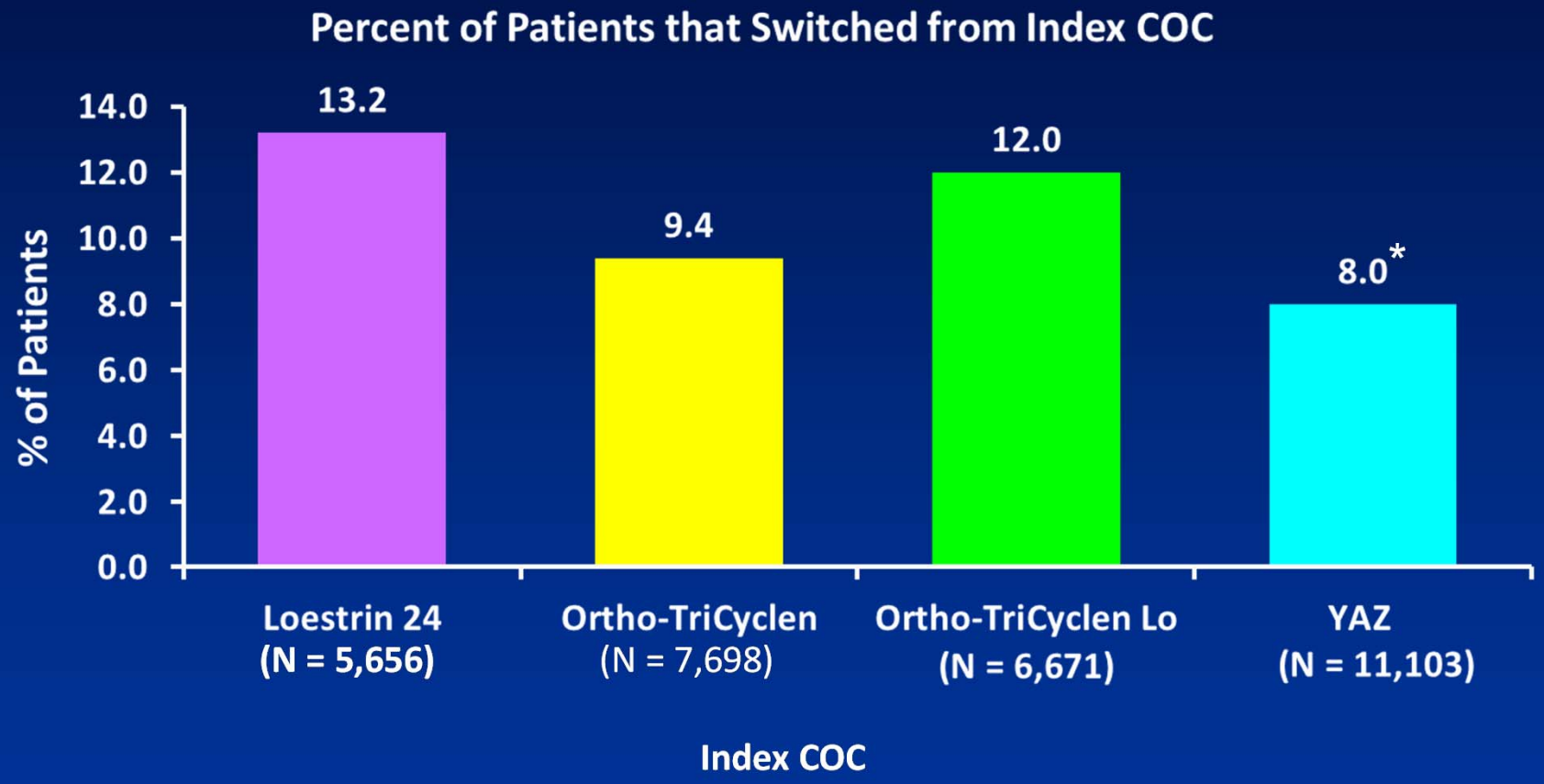
Dinger J et al, Obstet Gynecol 2011; 117:33-40

Yaz: Effect on Emotional and Physical Symptoms of PMDD



Pearlstein TB, et al, Contraception 2005; 72: 414-421

Yaz: Use Pattern Study in Marketscan Database (Jan 1 – Dec 31 2007)



*p<0.05 compared to all other groups

Law et al, Pharmacotherapy 2010; 30 (10) 427e – Abstract 219

CC-119

Nelson (2008): Prescription Refill Rates Up to 6 Months

	Number Starting*	Prescription Refill Rate (%) at		
		30 Days	90 Days	180 Days
Branded COCs	917,519	72.7	55.2	43.8
Yasmin	321,834	75.1	61.2	50.7

*Population recruited from October 2003 through December 2004.

Derived from Nelson et al, *Obstet Gynecol* 2008; 112 (4): 782 -787

Contraindications, Warnings and Precautions

Risk of VTE with COCs

Warnings and Precautions: Thromboembolic and Other Vascular Events

(An example consistent with label across recently approved COCs)*

Thromboembolic and Other Vascular Events: Stop Yaz if an arterial or venous thrombotic (VTE) event occurs. The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs.

The risk of venous thromboembolism in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Interim data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Interim data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued. If feasible, stop Yaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

* Yaz (Package Insert), section 5.1, March 2011

Variation in Point Estimates for VTE in Yasmin vs LNG-COC studies

Crude Incidence rates for Yasmin, LNG-COCs (and other COCs) across studies (per 10,000 WY)

	Yasmin	LNG-COC
EURAS	9.1	8.0
Lidegaard 2009	7.8	5.5
Lidegaard 2011	9.3	7.5
Jick 2011[#]	7.9	3.2
FDA study	7.6	6.6
LASS	10.7	9.2

Yasmin **1.4x**

LNG **2.9x**

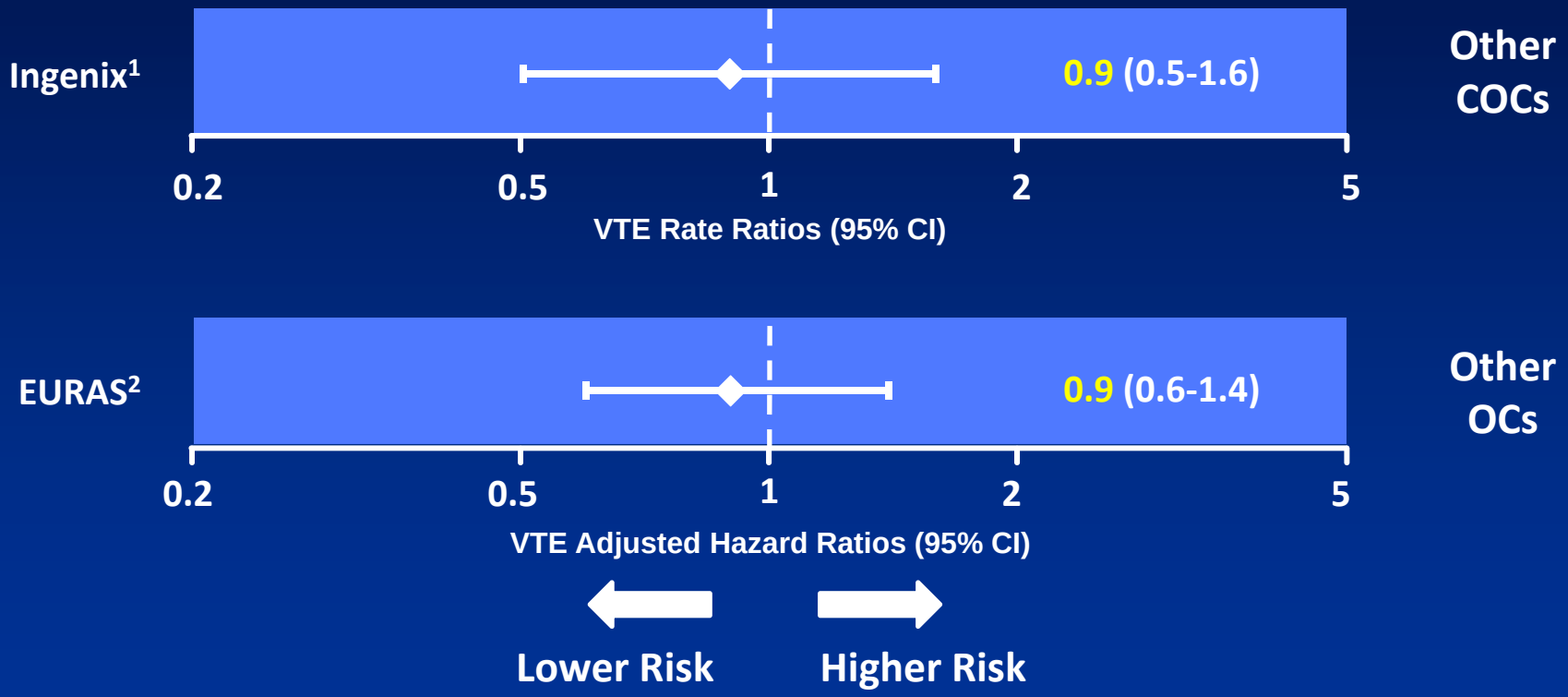
[#] extrapolated to idiopathic + non-idiopathic

CC-124

Chronological List of Reported Observational Studies on Yasmin and Risk of VTE

1. Dinger et al, 2007 (EURAS)
2. Seeger et al, 2007 (Ingenix)
3. Lidegaard et al, 2009 (Danish Registry)
4. van Hylckama Vlieg et al, 2009 (MEGA)
5. Dinger et al, 2010 (German Case-Control)
6. Jick et al, 2011 (PharMetrics)
7. Parkin et al, 2011 (GPRD)
8. Lidegaard et al, 2011 (“Re-analysis”)
9. FDA-funded study, 2011 (Kaiser and Medicaid)
10. LASS, 2011 (EURAS continuation)
11. Gronich et al, 2011 (Clalit)

Post-Approval Commitment Studies: Results



1. Seeger JD et al. *Obstet Gynecol*. 2007;110:587-593
2. Dinger JC et al. *Contraception*. 2007;75:344-354.

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Post-Approval Safety Studies: Ongoing Post-Approval Commitments

Study [ClinicalTrials.gov]	Type of Study	Post-Marketing Commitment (Regulatory Authority)
International Active Surveillance Study – Yaz (INAS-OC) [NCT00335257]	Prospective cohort	Yes (FDA + EMA)
International Active Surveillance Study – Natazia (INAS-SCORE) [NCT01009684]	Prospective cohort (recruiting)	Yes (FDA + EMA)
International Active Surveillance Study – Folate (INAS-FOCUS) [NCT01266408]	Prospective cohort (recruiting)	Yes (FDA)

Summary

- DRSP-COCs expand the range of available options and indications
- Risk of VTE with Yasmin similar to other COCs studied
  - Ingenix
  - EURAS + LASS
- Risk of ATE with Yasmin similar to (or possibly lower than) other COCs studied
- Interim data from the ongoing INAS study support that the risk of VTE for YAZ is similar to the other COCs studied

Conclusion

- DRSP-COCs are an important treatment for prevention of pregnancy and offer a favorable benefit-risk profile when used according to the US label

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